FORMULATION AND EVALUATION OF QUETIAPINE FUMARATE LOADED CARBOPOL 974P MUCOADHESIVE MICROSPHERES FOR THE TREATMENT OF SCHIZOPHRENIA

Dissertation Submitted to

The Tamil Nadu Dr. M.G.R. Medical University,

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In partial fulfillment for the award of Degree of

MASTER OF PHARMACY

(Pharmaceutics)

Submitted by

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MELMARUVATHUR - 603 319

MAY- 2012

CERTIFICATE

This is to certify that the dissertation entitled "**FORMULATION AND EVALUATION OF QUETIAPINE FUMARATE LOADED CARBOPOL 974P MUCOADHESIVE MICROSPHERES FOR THE TREATMENT OF SCHIZOPHRENIA"** submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfillment for the award of the Degree of the Master of Pharmacy (Pharmaceutics) was carried out by **A. SAMPATH (Register No. 26106007)** in the Department of Pharmaceutics under my direct guidance and supervision during the academic year 2011-2012.

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Dedicated To

My Beloved Parents, Friends

& All My Beloved Ones...

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CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

1. INTRODUCTION

1.1.Drug delivery systems (Y.W Chien., 2009)

The advancement of pharmacokinetics has established that the drug should be present above a certain minimum concentration in blood for as long a period as possible for optimum drug therapy.

Although, continuous infusion has been recognized as a superior mode of drug administration to maintain a constant and prolonged rug level in the body such mode of administration entails certain risk and hence requires hospitalization of the patient and close supervision.

As a result, solid oral dosage forms have become the most important and mostly used class of drug delivery system. Ordinary tablet and capsules known as conventional drug delivery system have to be administered several times a day depending on the biological half-life of the drug. Such multiple dosing may reduce invariably high plasma level of drug leading to waste of costly drugs and patient non-compliance.

Two important features as important while developing as drug delivery system. i.e., it should deliver the drug at a rate dictated by the needs of the body over the entire period of treatment and the drug should solely reach the site of action.

1.2.Sustained drug delivery systems (N.K.Jain., 2008)

The recognition of the fact that the absorption rate of the drugs into the body can be decreased by reduction of the rate of release of drug from the dosage forms. It leads to develop some system to release their medications to the body slowly for prolonged drug release and sustained drug action.

Current efforts in the area of drug delivery include the development of targeted delivery in which the drug in only active in the body (for example, in cancerous tissues) and sustained release formulations which the drug is released over a period of time in a controlled manner form a formulation. These of sustained release formulations include liposomes, drug loaded biodegradable microspheres and drug polymer conjugates.

1. Improve patient's compliance and convenience due to less frequent dosing of drug.
2. Reduced 'See-saw' fluctuation and therefore helps in better control of disease condition.
3. Maximum utilization drug enabling reduction in total amount of dose administered.
4. Reduction in health care cost through improved therapy, shorter treatment period and less frequency of dosing.

The problem frequently encountered is the is the increase the residence time of the dosage form in the stomach and proximal portion of the small intestine, due to the rapid gastrointestinal transit phenomenon of the stomach which may consequently diminish the extent of absorption of many drugs since almost most of the drug entities are

mostly absorbed from the upper part of the intestine, therefore it would be beneficial to develop a sustained release formulation which remain at the absorption site for an extended period of time.

Several approaches have been immersed to prolong the residence time of the dosage forms at the absorption site and one of these is the development of oral bioadhesive/mucoadhesive system. Various gastrointestinal mucoadhesive dosage forms, such as discs, microspheres, and bilayered tablets, have been thoroughly prepared and reported by several research groups.

1.3. Mucoadhesive drug delivery systems (Shobha rani., 2008)

Mucoadhesive drug delivery system is a new system of drug delivery and has recently gained great concern in pharmaceutical sciences. The concept of mucoadhesives was introduced in the early 1980s. Mucoadhesion can be defined as the phenomenon of the attachment of natural or synthetic polymers to a mucosal surface. In general, the process involved in the mucoadhesion phenomenon can be described in three steps: first of all, the wetting and swelling of the polymer should allow an intimate contact with the tissue and secondly, interpenetration of the polymer chains and entanglement between the polymer and the mucin chains should be attained and finally, the formation of weak chemical bonds. Mucus is a viscous and heterogeneous biological product that coats many epithelial surfaces. Mucus-secreting cells are widely spread in different locations in the body, including the nasal, ocular, buccal area and the gastrointestinal, reproductive and respiratory tracts. Mainly, the mucus serves as a lubricant to minimize shear stresses and as a protection barrier against harmful substances. However, mucus can perform other important functions. Goblet cells located in the epithelium are unicellular mucus-

secreting glands. Mucus is stored in large granules in the goblet cell and can be released by exocytosis or exfoliation of the whole cell. Mucus granules are mainly stored in the apical side of the goblet cell, which results in the characteristic balloon shape of these cells. Although the secretion of mucus can vary depending on age, sex, body location and health condition, the average mucus turnover is approximately 6 h. Mucus consists mainly of water (up to 95% weight), inorganic salts (about 1% weight), carbohydrates and lipids (less than 1%) and glycoproteins (no more than 5% weight). Mucus glycoproteins are also called mucins and consist of a protein core with branched oligosaccharide chains attached over 63% of its length. Approximately 80% by weight of the glycoprotein consists of oligosaccharides, which make the mucin more hydrosoluble and also protects the protein core from proteolytic degradation

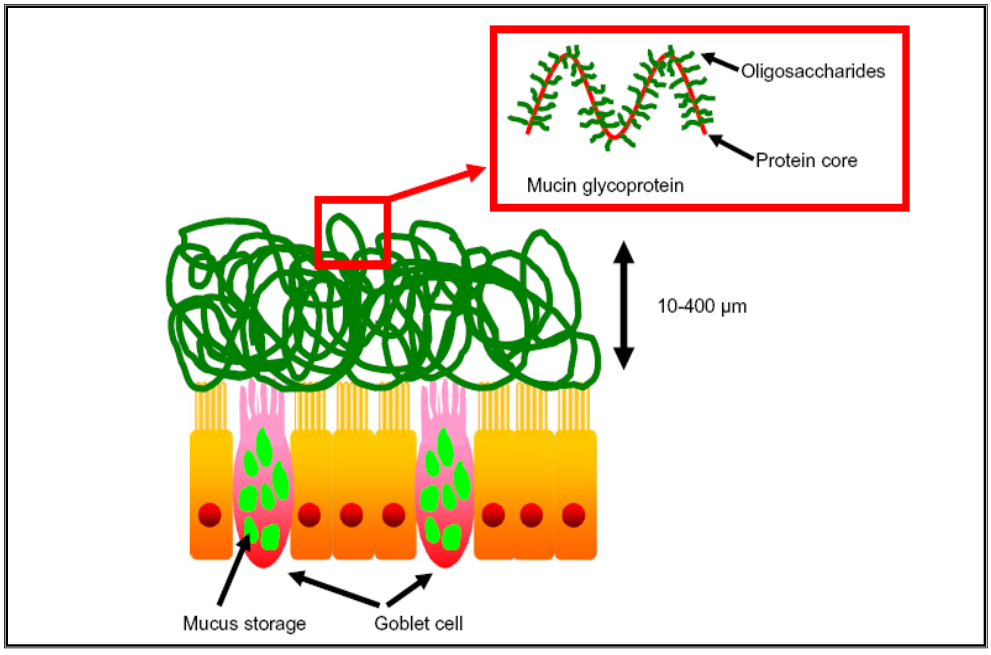


Figure 1.1: Mucus layer on epithelial surface

Bioadhesives are natural polymeric materials that act as adhesives. The term is sometimes used more loosely to describe glue formed synthetically from biological

monomers such as sugars, or to mean a synthetic material designed to adhere to biological tissue. The term bioadhesion refers to any bond formed between two biological surfaces or a bond between a biological and a synthetic surface. It may be defined as attachment of synthetic biological macromolecules to a biological tissue. A more specific term than bioadhesion is mucoadhesion.

Mucoadhesion is the relatively new and emerging concept in drug delivery. Mucoadhesion is the special case of bioadhesion where the biological tissue is an epithelium covered by mucus. Most mucosal surfaces such as in the gut or nose are covered by a layer of mucus.

Adhesion of a matter to this layer is hence called mucoadhesion. Mucoadhesion keeps the delivery system adhering to the mucus membrane.

Mucoadhesion can be defined as the ability of synthetic or biological macromolecules to adhere to mucosal tissues. The concept of mucoadhesion is one that has the potential to improve the highly variable residence times experienced by drugs and dosage forms at various sites in the gastrointestinal tract, and consequently, to reduce variability and improve efficacy.

These systems remain in close contact with the absorption tissue, the mucous membrane, releasing the drug at the site of action leading to an increase in bioavailability.

Mucoadhesive drug delivery system prolong the residence time of the dosage form at the site of application or absorption and facilitate an intimate contact of the dosage form with the underline absorption surface and thus contribute to improved and / or better therapeutic performance of the drug.

The mucoadhesive drug delivery system may include the following

1. Buccal delivery system.

2. Sublingual Delivery system.

3. Vaginal delivery system.

4. Rectal delivery system.

5. Nasal delivery system.

6. Ocular delivery system.

7. Gastro Intestinal delivery system

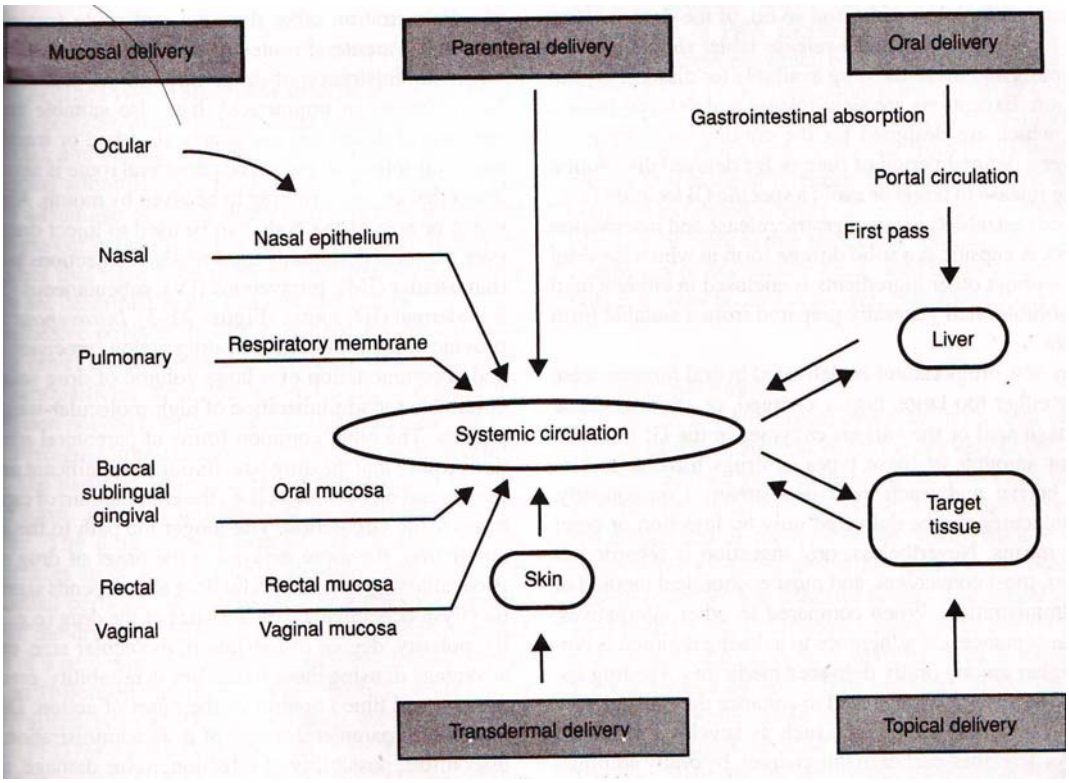


Figure 1.2. Potential sites for mucosal drug delivery

Their ability to stick to mucous membranes attracted attention as a pathway for resolving the problem of low bioavailability of traditional delivery systems used in the oral cavity and on the surface of the eye or other organs where movement of tissues or production of various secretions prevents prolonged retention of the medicinal agent. The

reasons that the oral route achieved such popularity may be in part attributed to its ease of administration as well as the traditional belief that by oral administration the drug is well absorbed as the food stuffs that are ingested daily.

In the exploration of oral controlled release drug administration, one encounters three areas of potential challenge.

1. Development of a drug delivery system: To develop a viable oral controlled release drug delivery system capable of delivering a drug at a therapeutically effective rate to a desirable site for duration required for optimal treatment.

2. Modulation of gastro intestinal transit time: To modulate the GI transit time so that the drug delivery system developed can be transported to a target site or to the vicinity of an absorption site and reside there for prolonged period of time to maximize the delivery of a drug dose.

3. Minimization of hepatic first pass elimination: If the drug to be delivered is subjected to extensive hepatic first pass elimination, preventive measures should be devised to either bypass or minimize the extent of hepatic metabolic effect.

Definition of mucoadhesion (Amit Alexander., 2011)

Adhesion can be defined as the bond produced by contact between a pressure - sensitive adhesive and a surface The American Society of testing and materials has defined it as the state in which two surfaces are held together by interfacial forces, which may consist of valence forces, interlocking action or both. When the adhesion involves mucus or mucus membrane it is termed as mucoadhesion.

Concepts of mucoadhesion

In biological systems, four types of bioadhesion can be distinguished as follows:-

1. Adhesion of a normal cell on another normal cell.

2. Adhesion of a cell with a foreign substance.

3. Adhesion of a normal cell to a pathological cell.

4. .Adhesion of an adhesive to a biological substance.

Mucous membrane

Mucous membranes are the moist linings of the orifices and internal parts of the body that are in continuity with the external surface. They cover, protect, and provide secretory and absorptive functions in the channels and extended pockets of the outside world that are incorporated in the body. Mucus is a translucent and viscid secretion, which forms a thin, continuous gel blanket adherent to mucosal epithelial surface. The mean thickness of this layer varies from about 50-450 μm in humans. It is secreted by the goblet cells lining the epithelia or by special exocrine glands with mucus cells acini. The exact composition of the mucus layer varies substantially, depending on the species, the anatomical location and pathological states. They secrete a viscous fluid known as mucus, which acts as a protective barrier and also lubricates the mucosal membrane. Mucosal membranes of human organism are relatively permeable and allow fast drug absorption They are characterized by an epithelial layer whose surface is covered by mucus. The primary constituent of mucus is a glycoprotein known as mucin as well as water and inorganic salts. However, it has general composition.

Table 1.1: Composition of Mucous Membrane

S.NO.	COMPOSITION	% AMOUNT
1	Water	95
2	Glycoproteins & Lipids	0.5-5.0
3	Mineral Salts	1
4	Free Proteins	0.5-1.0

Table 1.2: Comparative properties of gastrointestinal, Dermal and Transmucosal drug administration (Khar, et al., 2003)

	Gastrointestinal	Dermal	Nasal	Oral mucosal	Vaginal
Accessibility	+	+++	++	++	+
Surface area	+++	+++	+	++	+++
Surface Environment	+	++	++	+++	+
Permeability	+++	+	+++	++	+++
Reactivity	++	++	+	+++	++
Vascular Drainage	+++	+	+++	++	+++
First pass clearance	+	+++	+++	+++	+
Patient acceptability	++	+++	++	+++	+++

Examples of mucosa

· Buccal mucosa.

· Oesophageal mucosa.

· Gastric mucosa.

· Intestinal mucosa.

· Nasal mucosa.

· Olfactory mucosa.

· Oral mucosa.

· Bronchial mucosa.

· Uterine mucosa.

· Endometrium (mucosa of the uterus).

· Penile mucosa.

1.4 Mucoadhesive polymers

Mucoadhesive polymers are water-soluble and water-insoluble polymers, which are swellable networks, jointed by cross-linking agents. These polymers possess optimal polarity to make sure that they permit sufficient wetting by the mucus and optimal fluidity that permits the mutual adsorption and interpenetration of polymer and mucus to take place.

Mucoadhesive polymers that adhere to the musin-epithelial surface can be conveniently divided into three broad classes,

1) Polymers that become sticky when placed in water and owe their muco- adhesion to stickiness.

2) Polymers that adhere through nonspecific, noncovalent interactions are primarily electrostatic in nature (although hydrogen and hydrophobic bonding may be significant).

3) Polymers that bind to specific receptor site on tile self surface.

Examples of some Mucoadhesive polymer

Natural /Semi-synthetic	Na alginate,	Agarose,	Chitosan,
	Pectin,	Tragacanth,	Gelatin,
	Xanthan gum,	Carragenan,	Starch
Synthetic	Poly vinyl alcohol,	Polyamides,	Polycarbonates,
	Poly alkylene glycols,	Poly vinyl ethers,	Esters and halides
	Poly methacrylic acid,	PMMA,	Methyl cellulose,
	Ethyl cellulose,	HPC,	HPMC
	Methyl cellulose,	Sod. CMC	
Bicompatible	Esters of haluronic acid,		
	Polyvinyl acetate,		
	Ethylene glycol.		
Biodegradable	Poly (lactides),	Poly (lactide-coglycolides),	
	Poly caprolactones,	Poly alkyl cyanoacrylates.	
	Poly orthoesters,	Poly (glycolides),	
	Poly phosphoesters,	Poly anhydrides,	
	Poly phosphazenes,	Chitosan,	

Ideal characteristics of a mucoadhesive polymer

1. The polymer and its degradation products should be nontoxic and nonabsorable from the GIT.
2. It should be nonirritant to the mucous membrane.
3. It should preferably form a strong noncovalent bond with the mucin-epithelial cell surfaces.
4. It should adhere quickly to most tissue and should possess some site-specificity.
5. It should allow daily incorporation to the drug and offer no hindrance to its release.
6. The polymer must not decompose on storage or during the shelf life of the dosage form.
7. The cost of polymer should not be high so that the prepared dosage form remains competitive.

1.5. Factors affecting mucoadhesion

1) Polymer Related Factors

a) Molecular weight: The interpenetration of polymer molecules into the mucus layer is variable, for low molecular weight polymers penetration is more than high molecular weight polymers because entanglements are favored in high molecular weight polymers.

b) Concentration of active polymer: For solid dosage forms such as tablets, the higher the concentration of polymer, the stronger the bioadhesion force.

c) Spatial Conformation: Bioadhesive force is also dependent on the conformation of polymers, i.e., helical or linear. The helical conformation of polymers may shield many

active groups, primarily responsible for adhesion, thus reducing the mucoadhesive strength of the polymer.

d) Chain flexibility of polymer: Chain flexibility is important for interpenetration and enlargement. As water-soluble polymers become more and more cross linked, the mobility of the individual polymer chain decreases, also as the cross linking density increases, the effective length of the chain which can penetrate into mucus decrease even further and mucoadhesive strength is reduced.

e) Degree of Hydration: Another important factor affecting the mucoadhesive strength of polymeric components is the degree of hydration. In this respect many polymers will exhibit adhesive properties under conditions where the amount of water is limited. However in such a situation, adhesion is thought to be a result of a combination of capillary attraction and osmotic forces between the dry polymer and the wet mucosal surface which act to dehydrate and strengthen the mucus layer. Although this kind of "sticking" has been referred to as mucoadhesion it is important to clearly distinguish such processes from "wet-on-wet" adhesion in which swollen mucoadhesive polymers attach to mucosal surfaces. Hydration is essential for the relaxation and interpenetration of polymer chains, excess hydration could lead to decreased mucoadhesion and/orientation due to the formation of slippery mucilage. In this situation cross linked polymers that only permit a certain degree of hydration may be advantageous for providing a prolonged mucoadhesive effect. The attachment and bonding of bioadhesive polymers to biological substrates occurs mainly through interpenetration followed by secondary non-covalent bonding between substrates. Given that secondary bonding mainly arises due to hydrogen bond formation, it is well accepted that mucoadhesive polymers possessing hydrophilic

functional such as, carboxyl (COOH), hydroxyl (OH), amide (NH2) and sulphate groups (SO4H) may be more favorable in formulating targeted drug delivery platforms. Typically, physical entanglements and secondary interactions (hydrogen bonds) contribute to the formation of a strengthened network; therefore polymers that exhibit a high density of available hydrogen bonding groups would be able to interact more strongly with mucin glycoproteins.

2) Environmental – Related Factors

a) pH: pH influences the charge on the surface of both mucus and polymers. Mucus will have a different charge density depending on pH, because of difference in dissociation of functional groups on carbohydrate moiety and amino acids of the polypeptide backbone, which may affect adhesion.

b) Applied strength: To place a solid bioadhesive system, it is necessary to apply a defined strength. Whichever the polymer may be the adhesion strength of those polymers increases with the increase in the applied strength.

c) Initial contact time: The initial contact time between mucoadhesive and the mucus layer determines the extent of swelling and the interpenetration of polymer chains. The mucoadhesive strength increases as the initial contact time increases.

d) Selection of the model substrate surface: The handling and treatment of biological substrates during the testing of mucoadhesive is an important factor, since physical and biological changes may occurs in the mucus gels or tissues under the experimental conditions.

3) Swelling: The swelling characteristic is related to the polymer itself, and also to its environment. Interpenetration of chains is easier as polymer chains are disentangled and

free of interactions. More the swelling of polymeric matrix higher the adhesion time of polymers.

4) Physiological variables:

Mucin turnover and disease state of mucus layer are physiological variables, which may affect bioadhesion.

Functions of mucous layer (N.K.Jain ., 1997)

The mucous layer, which covers the epithelial surface, has various roles.

1. Protective Role.
2. Barrier Role.
3. Adhesion Role.
4. Lubrication Role.
5. Mucoadhesion Role.

1. **Protective Role:** The Protective role results particularly from its hydrophobicity and protecting the mucosa from the lumen diffusion of hydrochloric acid from the lumen to the epithelial surface.

2**. Barrier Role:** The role of mucus layer as barrier in tissue absorption of drugs and other substances is well known as it influence the bioavailibity of the drugs.The mucus constitutes diffusion barrier for molecules, and especially against drug absorption diffusion through mucus layer depends on molecule charge, hydration radius, ability to form hydrogen bonds and molecular weight

3. **Adhesion Role:** Mucus has strong cohesive properties and firmly binds the epithelial cells surface as a continuous gel layer.

4. **Lubrication Role:** An important role of the mucus layer is to keep the membrane moist. Continuous secretion of mucus from the goblet cells is necessary to compensate for the removal of the mucus layer due to digestion, bacterial degradation and solubilisation of mucin molecules

5. **Mucoadhesion Role:** One of the most important factors for bioadhesion is tissue surface roughness. Adhesive joints may fail at relatively low applied stresses if cracks, air bubbles, voids, inclusions or other surface defects are present. Viscosity and wetting power are the most important factors for satisfactory bioadhesion.

At physiological pH, the mucus network may carry a significant negative charge because of the presence of sialic acid and sulphate residues and this high charge density due to negative charge contributes significantly to the bioadhesion.

Need of mucoadhesive

- Controlled release.
- Target & localised drug delivery.
- By pass first pass metabolism.
- Avoidance of drug degradation.
- Prolonged effect.
- High drug flux through the absorbing tissue.
- Reduction in fluctuation of steady state plasma level.
    - An ideal dosage form is one, which attains the desired therapeutic concentration of drug in plasma and maintains constant for entire duration of treatment. This is possible through administration of a conventional dosage form in a particular dose and at particular frequency. In most cases,

the dosing intervals much shorter than the half life of the drug resulting in a number of limitations associated with such a **conventional dosage** form are as follows:

- Poor patient compliance; increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.
- A typical peak plasma concentration time profile is obtained which makes attainment of steady state condition difficult.
- The unavoidable fluctuation in the drug concentration may lead to under medication or over medication as the steady state concentration values fall or rise beyond in the therapeutic range.
- The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index whenever overmedication occurs

Advantages of mucoadhesives (S.Punitha and S.Ganga., 2007)

- A prolonged residence time at the site of drug action or absorption.
- A localization of drug action of the delivery system at a given target site.
- An increase in the drug concentration gradient due to the intense contact of particles with the mucosal.
- A direct contact with intestinal cells that is the first step before particle absorption.
- Ease of administration.
- Termination of therapy is easy.{except gastrointestinal}
- Permits localization of drug to the oral cavity for a prolonged period of time.
- Can be administered to unconscious patients. Except gastrointestinal}

- Offers an excellent route, for the systemic delivery of drugs with high first pass metabolism, there by offering a greater bioavailability
- A significant reduction in dose can be achieved there by reducing dose related side effects.
- Drugs which are unstable in the acidic environment are destroyed by enzymatic or alkaline environment of intestine can be administered by this route. Eg. Buccal sublingual, vaginal.
- Drugs which show poor bioavailability via the oral route can be administered conveniently. It offers a passive system of drug absorption and does not require any activation.
- The presence of saliva ensures relatively large amount of water for drug dissolution unlike in case of rectal and transdermal routes.
- Systemic absorption is rapid.
- This route provides an alternative for the administration of various hormones, narcotic analgesic, steroids, enzymes, cardiovascular agents etc.\
- The buccal mucosa is highly perfused with blood vessels and offers a greater permeability than the skin.
- Less dosing frequency.
- Shorter treatment period.
- Increased safety margin of high potency drugs due to better control of plasma levels.
- Maximum utilization of drug enabling reduction in total amount of drug administered.

- Improved patient convenience and compliance due to less frequent drug administration.
- Reduction in fluctuation in steady state levels and therefore better control of disease condition and reduced intensity of local or systemic side effects.
- Despite the several advantages associated with oral controlled drug delivery systems, there are so many **disadvantages,** which are as follows:
- Basic assumption is drug should absorbed throughout GI tract
- Limited gastric residence time which ranges from few minutes to 12 hours which lead to unpredictable bioavailability and time to achieve maximum plasma level.

1.6. Limitations of mucoadhesion

- Drug administration via the buccal mucosa has certain limitations
- Drugs, which irritate the oral mucosa, have a bitter or unpleasant taste, odour, cannot be administered by this route.
- Drugs, which are unstable at buccal pH cannot be administered by this route.
- Only drugs with small dose requirements can be administered.
- Drugs may swallow with saliva and loses the advantages of buccal route.
- Only those drugs, which are absorbed by passive diffusion, can be administered by this rout.
- Eating and drinking may become restricted.
- Swallowing of the formulation by the patient may be possible.
- Over hydration may lead to the formation of slippery surface and structural integrity of theformulation may get disrupted by the swelling and hydration of the bioadhesive polymers.

1.7. Stages of mucoadhesion (S. P. Vyas.,2002)

1. Contact Stage
2. Consolidation Stage.

- **Contact Stage:** The first stage is characterized by the contact between the mucoadhesive and the mucous membrane, with spreading and swelling of the formulation, initiating its deep contact with the mucus layer.
- **Consolidation Stage:** In the consolidation step (Figure 1), the mucoadhesive materials are activated by the presence of moisture. Moisture plasticizes the system, allowing the mucoadhesive molecules to break free and to link up by weak Vander Waals and hydrogen bonds.

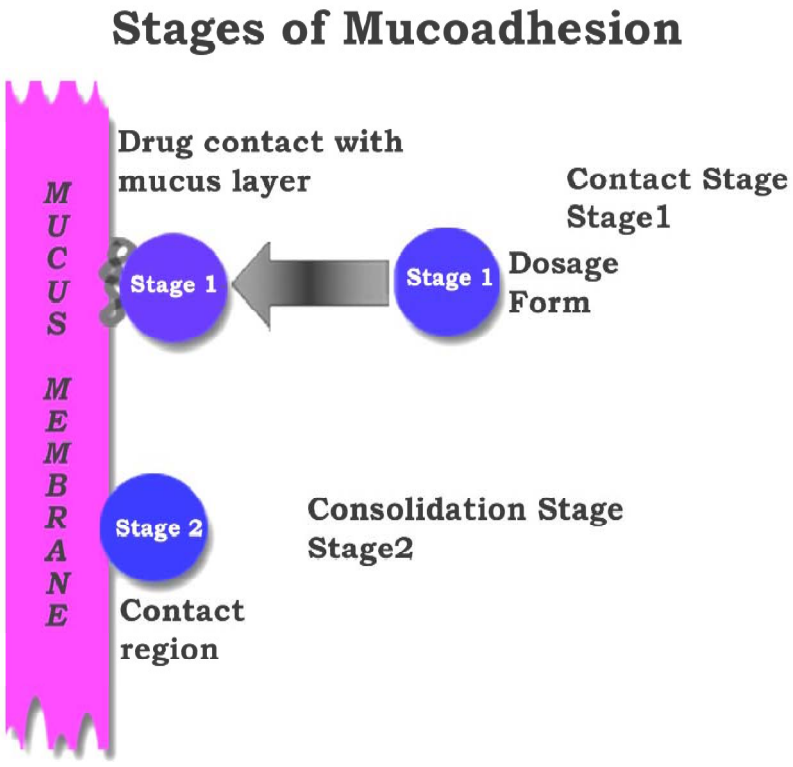


Figure 1.3: The two steps of the mucoadhesion process

1.8. Theories of mucoadhesion *(Jain N.K., et al., 2004)*

1. Electronic Theory

The adhesive polymer and mucus membrane strategically have different electronic characteristics. When the two surfaces contact each other, a double layer of electrical charge is formed at the interface, and then adhesion developed between the double layers due to electrical charge.

2. Adsorption Theory

The adsorption theory of bioadhesion proposes two bond theories:

(i) Primary chemical bonds permanent and therefore undesirable in bioadhesion

(ii) Secondary chemical bonds are found to be van-der Waals, hydrogen, hydrophobic and electrostatic forces.

3. Wetting Theory

The wetting theory emphasizes mainly on the intimate contact between the adhesive and mucus. Thus, a wetting surface will be controlled by structural similarity, degree of cross linking of the adhesive polymer, or use of a surfactant.

4. Diffusion Theory

A semi permanent adhesive bond is formed because of the chains of adhesive and the substrate interpenetrates one another to a sufficient depth and it is considered as the essence of this theory. The diffusion coefficient of both interacting polymers and the diffusion co-efficient are the factors responsible for the penetration rate. In addition mobility, flexibility of the bioadhesive polymer, mucus glycoprotein, and the expanded nature of both network are other important parameters considered.

1.9. Mechanism of mucoadhesion (J.H.Bhatt and Aidoo., 2009)

The concept of mucoadhesion is one that has the potential to improve the highly variable residence times experienced by drugs and dosage forms at various sites in the gastrointestinal tract, and consequently, to reduce variability and improve efficacy. Intimate contact with the mucosa should enhance absorption.

The mechanisms responsible in the formation of bioadhesive bonds are not fully known, however most research has described bioadhesive bond formation as a three step process.

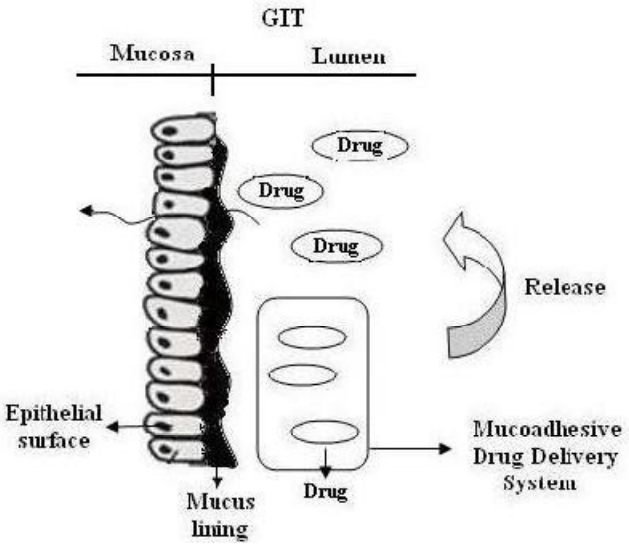


Figure 1.4: Interaction of mucoadhesive drug delivery system with mucous layer

STEP 1: Wetting and swelling of polymer

STEP 2: Interpenetration between the polymer chains and the mucosal membrane.

STEP 3: Formation of Chemical bonds between the entangled chains**.**

- **Step 1**

The wetting and swelling step occurs when the polymer spreads over the surface of the biological substrate or mucosal membrane in order to develop an intimate contact with the substrate.

This can be readily achieved for example by placing a bioadhesive formulation such as a tablet or paste within the oral cavity or vagina. Bioadhesives are able to adhere to or bond with biological tissues by the help of the surface tension and forces that exist at the site of adsorption or contact. Swelling of polymers occurs because the components within the polymers have an affinity for water.

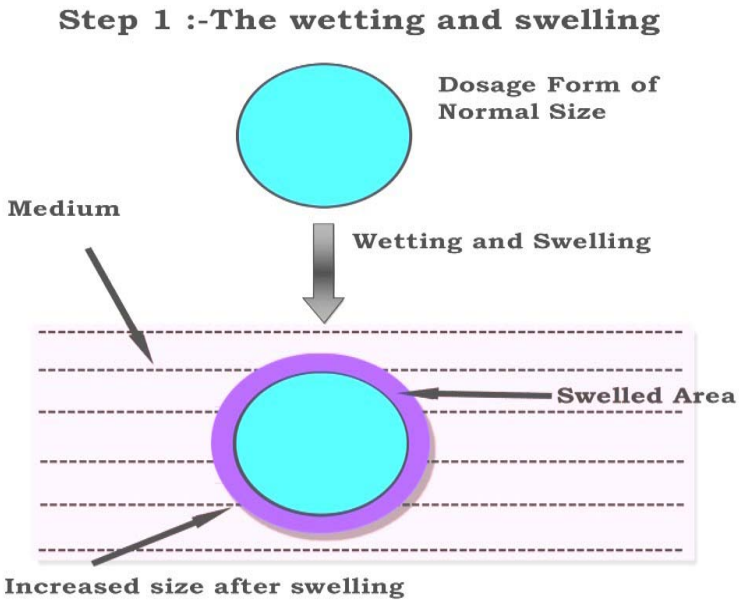


Figure 1.5: Wetting and Swelling of Polymer

- **Step 2**

The surface of mucosal membranes is composed of high molecular weight polymers known as glycoproteins. In this step interdiffusion and interpenetration take place between the chains of mucoadhesive polymers and the mucous gel network creating a great area of contact. The strength of these bonds depends on the degree of penetration between the two polymer groups. In order to form strong adhesive bonds, one polymer

group must be soluble in the other and both polymer types must be of similar chemical structure.

Interdiffusion and interpenetration

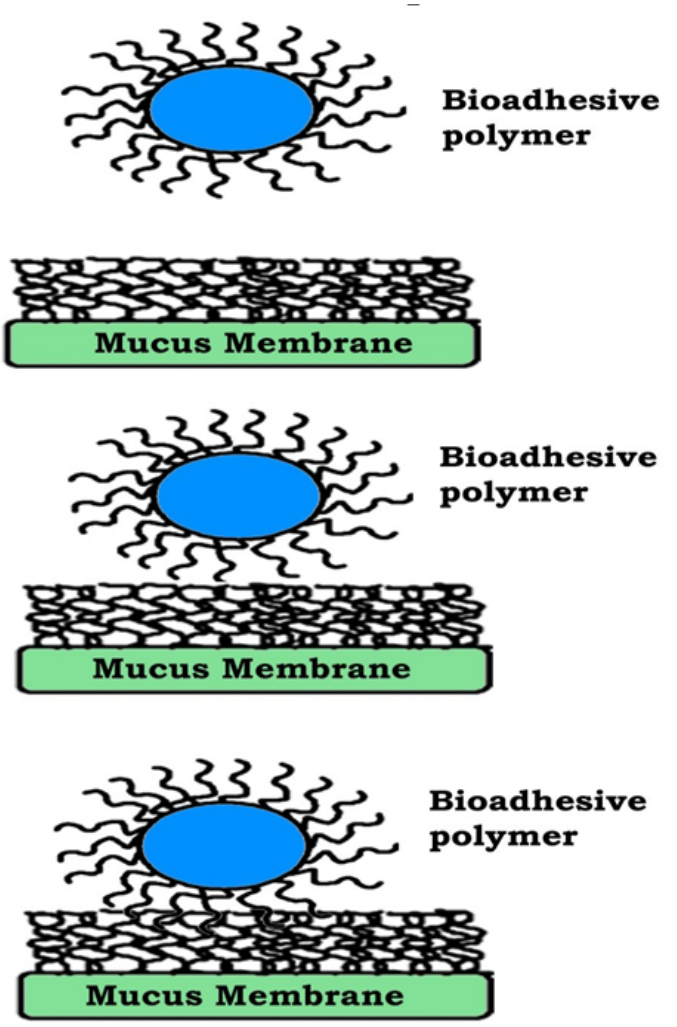


Figure 1.6: Interdiffusion and Interpenetration of Polymer and Mucus

- **Step 3**

In this step entanglement and formation of weak chemical bonds as well as secondary bonds between the polymer chains mucin molecule The types of bonding formed between the chains include primary bonds such as covalent bonds and weaker secondary interactions such as van-der Waals Interactions and hydrogen bonds. Both

primary and secondary bonds are exploited in the manufacture of bioadhesive formulations in which strong adhesions between polymers are formed.

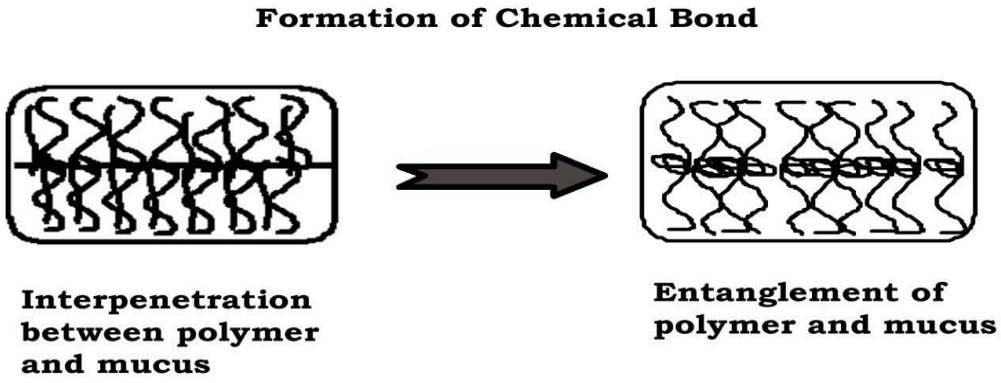


Figure.1.7: Entanglement of Polymer and Mucus by Chemical bonds

1) **Ionic bonds**—where two oppositely charged ions attract each other via electrostatic interactions to form a strong bond (e.g. in a salt crystal).

2) **Covalent bonds**—where electrons are shared, in pairs, between the bonded atoms in order to fill the orbital in both. These are also strong bonds.

3) **Hydrogen bonds**—here a hydrogen atom, when covalently bonded to electronegative atoms such as oxygen, fluorine or nitrogen, carries a slight positively charge and is therefore is attracted to other electronegative atoms. The hydrogen can therefore be thought of as being shared, and the bond formed is generally weaker than ionic or covalent bonds.

4) Van-der-Waals bonds—these are some of the weakest forms of interaction that arise from dipole– dipole and dipole-induced dipole attractions in polar molecules, and dispersion forces with non-polar substances.

5) Hydrophobic bonds—more accurately described as the hydrophobic effect, these are indirect bonds (such groups only appear to be attracted to each other) that occur when

non-polar groups are present in an aqueous solution. Water molecules adjacent to non-polar groups form hydrogen bonded structures, which lowers the system entropy.

Micro particles are of two types *(*Khar *R.K., et al., 2002)*

1. *Microspheres:* "The adsorbed substance is dispersed throughout the microsphere matrix".

2. *Micrcapsules:* "The entrapped substance is completely surrounded by a distinct" capsule wall.

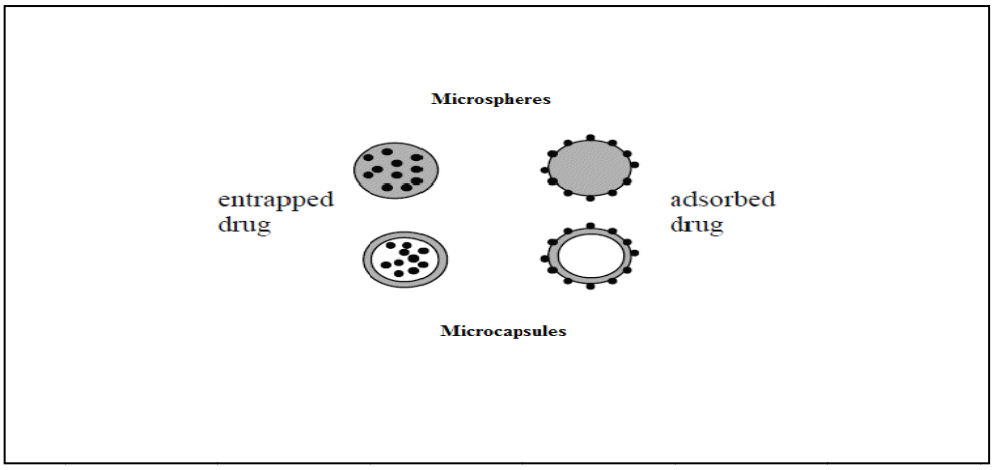


Figure 1.8: Differentiation between microspheres and microcapsules

1.10. Loading of drug

The active components are loaded on to the microspheres principally using two methods either during the preparation or after the formation of microsphere by incubating them with drug.

The active components can be loaded by means of physical entrapment, chemical linkage or surface absorption. Entrapment largely depends on the method of preparation and the nature of drug and polymer.

Maximum loading can be achieved by incorporating the drug at the time of preparation but it may get affected by many other process variables such as method of preparation, presence of additives heat of polymerization, agitation intensity etc. drug in loading in pre-formed microspheres is relatively less but the major advantage of the loading method is that there is no effect of process variables, loading is carried out in preformed microsphere by incubating them with high concentration of drug in a suitable solvent. The drug in these microspheres is loaded by penetration or diffusion through the pores.

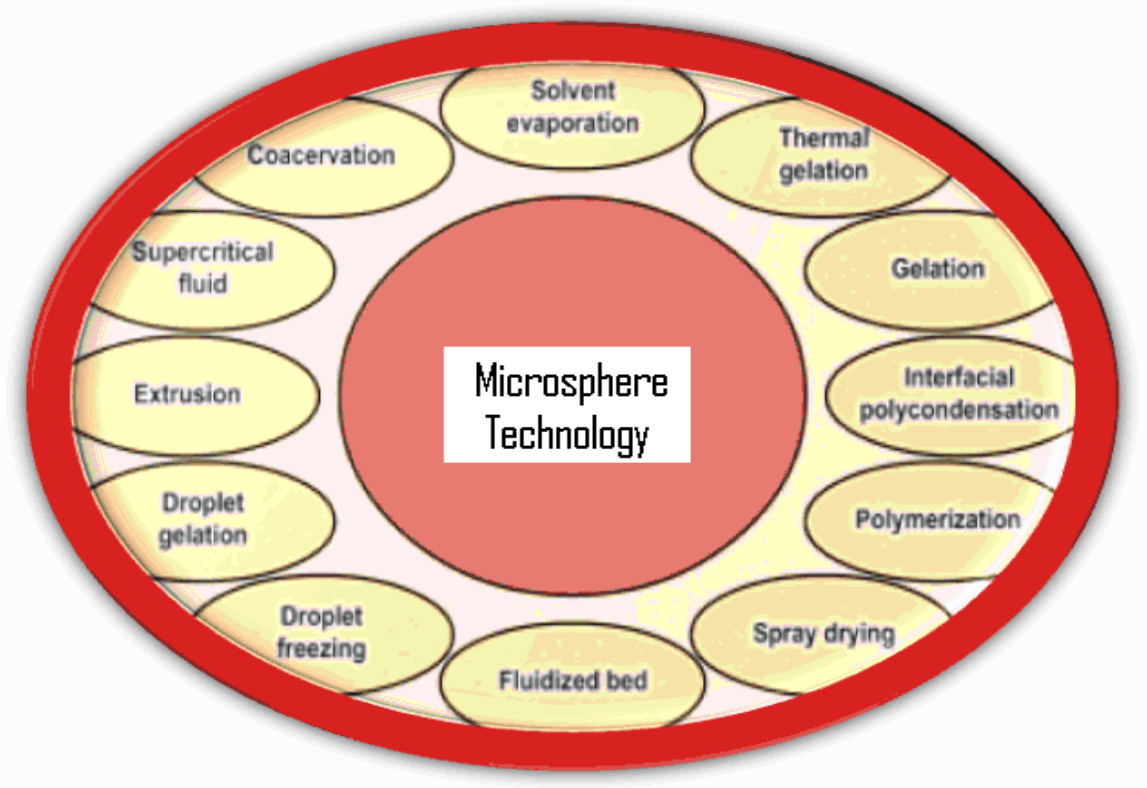


Figure 1.9: Different methods employed for microspheres

1.11. Methodology *(Belgamwar ., 2010)*

The selected methods of Mucoadhesive microspheres was prepared by,

Ionic Orifice Gelation Technique

In this technique cross linking of sodium alginate is done with calcium chloride solution to release the drug in a controlled manner. Chemically alginates are anionic block co-polymer consisting monomers of d – mannoic acid joined together by 1-4 glycosidic linkages. Bivalent alkaline earth metals like calcium undergoes ionic interaction with COOH moiety of sodium alginate and results in cross linking of sodium alginate. Microspheres were prepared by using the technique in which sodium alginate in different ratios as mentioned then added mucoadhesive polymers was slowly added to the above solution with continuous stirring to form homogenous solution.

After the aqueous sodium alginate solution by sonicating the mixture for 20 minutes the drug substance Quetiapine fumarate was then added to the above solution to form a clear solution (polymer – alginate mixture). The drug polymer mixture is dispersion was poured in 15% calcium chloride solution using 22# needle by stirring at 50rpm the microspheres thus formed are allowed 30 min for curing in calcium chloride solution then were decanted and washed with distilled water and air dried over night at room temperature.

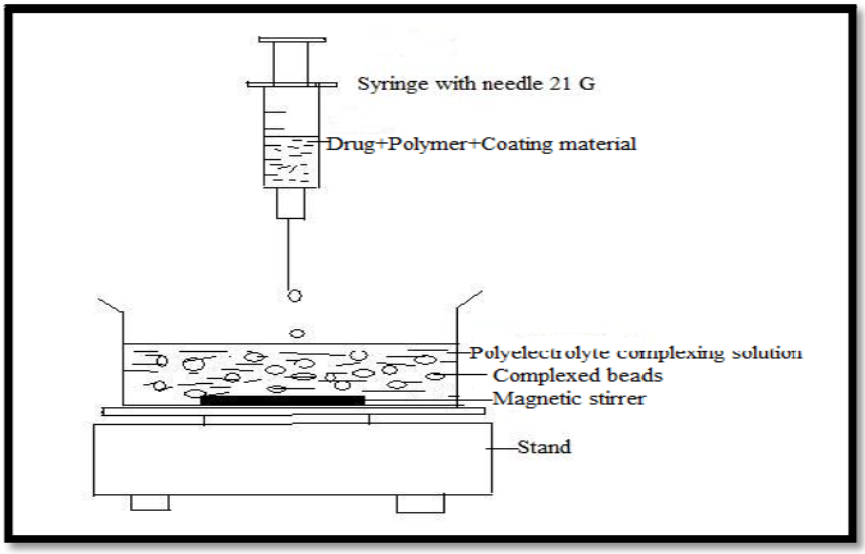


Figure 1.10: Beads prepared by the ionotropic gelation method

1.12. Techniques to manufacture microspheres *(Robinson J.R.,1985)*

A. Physical methods

Air-suspension coating

The particles are coated while suspended in an upward-moving air flow stream. Just sufficient air is only permitted to rise through the outer annular space to fluidize the particles settling. Most of the rising air (usually heated) flows inside around the cylinder, causing the particles rising rapidly.

At the top surface, as the air stream diverges and slows, they settle back onto the outer bed and move downward to repeat the cycle. In this process, has the ability of applying coatings in the form of solvent solutions, aqueous solution, emulsions, and dispersions. Core materials comprised of micron particles can be effectively encapsulated by air suspension techniques, but agglomeration of the particles to some larger size is achieved.

Coacervation-Phase Separation

The general outline of the processes consists of three steps carried out under continuous agitation.

1**. Formation of three immiscible chemical phases**

A liquid manufacturing phase, a core material and a coating material. To form the three phases, the core material dispersed in a solution of the coating polymer, the solvent for the polymer being the liquid manufacturing vehicle phase.

2. **Deposition of the coating**

It is mainly of depositing the liquid polymer coating upon the core material. This is obtained by controlled, physical mixing of the material in the manufacturing vehicle. Deposition of the liquid polymer coating around the core material occurs only if the polymer is adsorbed at the interface between the core material and the liquid vehicle phase. The continued deposition of the coating material is improved by a reduction in the total free interfacial energy of the system.

3**. Rigidization of the coating**

It involves mainly in rigidizing the coating, usually by thermal, cross-linking, or desolvation techniques, to form a self-sustaining microspheres.

Pan coating

The pan coating process, mainly used in the pharmaceutical industry, is among the oldest industrial procedures for forming small, coated particles or tablets. The particles are mainly tumbled in a pan or other device while the coating material is applied steadily and slowly. The particles has been tumbled in pan, while the coating material is applied slowly with respect to microspheres, solid particles are greater.

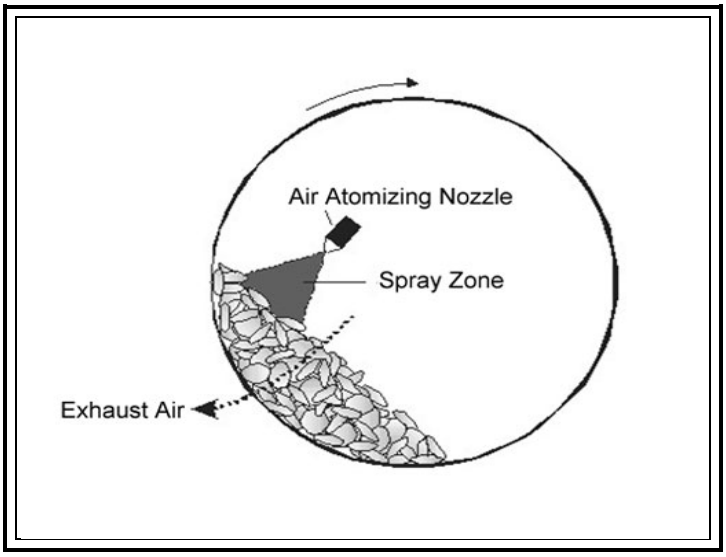


Figure 1.11: Pan coating and its process

Spray–drying

Spray drying is an important microspheres technique in this an active material is dissolved or suspended in a melt or polymer solution and becomes trapped in the dried particle. The main advantages of this ability to handle labile materials because of the short contact time in the dryer, in addition, the operation is economical. In modern spray dryers, the solutions are to be sprayed can be as high as 300mPa.s. Spray drying and spray congealing processes are similar in that both involve dispersing the core material in a liquid coating substance and spraying the core - coating mixture into some environmental condition, whereby relatively rapid solidification (and formation) of the coating is affected. The principal difference between the two methods is the coating solidification is obtained.

Coating solidification in the case of spray drying is effected by rapid evaporation of a solvent, by thermally congealing a molten coating material or by solidifying a dissolved coating by introducing the coating - core material mixture into a non-solvent.

Removal of the non-solvent or solvent from the coated product is then accomplished by sorption, extraction, or evaporation techniques.

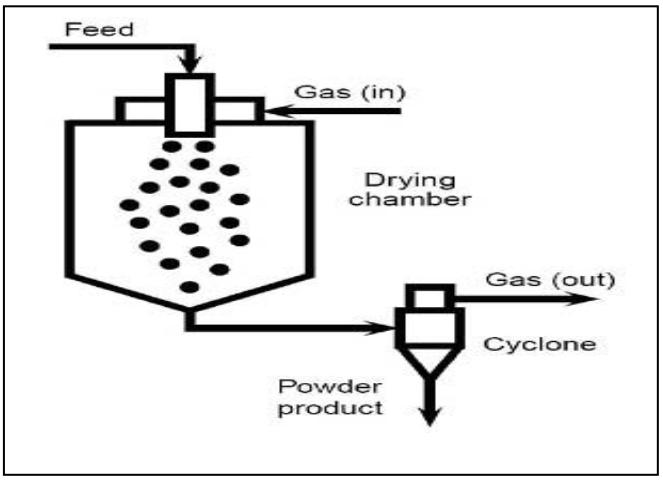


Figure 1.12: Spray drying technique and its process

Chemical process

Solvent Evaporation

The liquid manufacturing vehicle is the mainly used for the formulation. The coating for the microspheres will be dissolved in a volatile solvent, which has to be immiscible with the liquid manufacturing vehicle phase. A core material will be either dissolved or dispersed in the coating polymer solution. On agitation, the core coating material mixture will be dispersed in the liquid manufacturing vehicle phase to obtain the microspheres of appropriate size. The mixture will be then heated (if necessary) to evaporate the solvent in the polymer. In the case in which the core material is dispersed in the polymer solution, polymer shrinks around the core.

In the case in which core material is dissolved in the coating polymer solution, a matrix - type microsphere is formed. Once all the solvent evaporated, the liquid vehicle temperature is reduced to ambient temperature (if required) with continued agitation. At this stage, the microspheres can also be used in suspension form, coated on to substrates or isolated as powders.

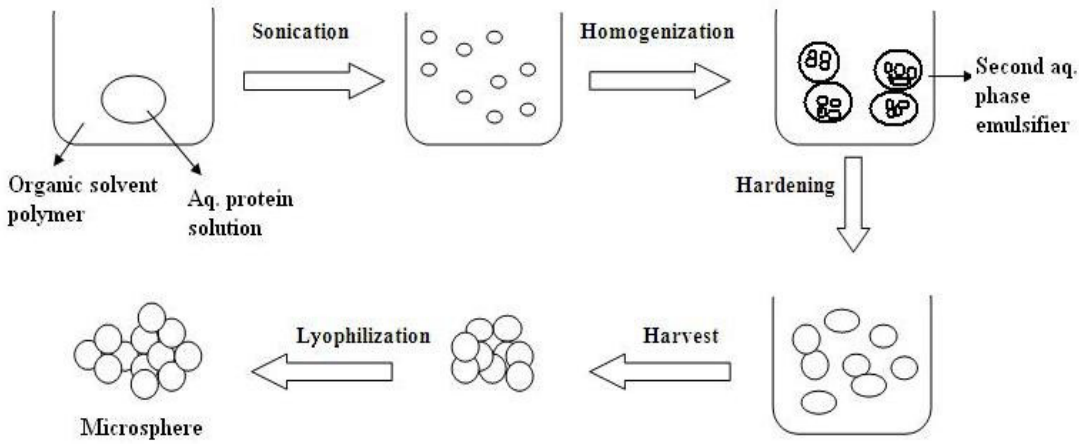


Figure 1.13: Solvent evaporation process

The solvent evaporation technique is used to produce microspheres which are applicable to a wide variety of liquid and solid core materials. The core materials may be either water - soluble or water - insoluble materials. e.g. "Evaluation of Sucrose Esters as Alternative Surfactants in Microspheres of Proteins by the Solvent Evaporation Method".

Centrifugal extrusion

Liquids are been encapsulated using a rotating extrusion head containing concentric nozzles. In this particular process, a core liquid is surrounded by a sheath of wall solution or melt. As the jet moves through the air it will break, owing to Rayleigh instability, core droplets are formed, each coated with the wall solution. From the droplets formed, a molten wall will be hardened or a solvent may be evaporated from the

wall solution. This process is excellent for forming making particles 400–2,000 μm (16–79 mils) in diameter.

Vibrational Nozzle

Micro granulation (matrix-encapsulation) can be done by using a laminar flow through a nozzle and an additional vibration of the nozzle. The vibration has to be done in resonance and Rayleigh instability leads to form uniform droplets. The liquid should be with limited viscosities (0-10,000 mPa·s have been shown to work), e.g. solutions, emulsions, suspensions, melts etc. The solidification can be done with an internal gelation (e.g. sol-gel processing, melt) or an external (additional binder system, e.g. in a slurry). The process works for generating droplets between 100–5,000 μm (3.9–200 mils), for preparing smaller and larger droplets are known.

Interfacial polymerization

In Interfacial polymerization, Polycondensation of the two reactants occur in between. The basis of this method termed as the classical Schotten-Baumann reaction between compound an acid chloride containing an active hydrogen atom, such as an amine or alcohol, polyesters, polyurea, polyurethane.

Matrix polymerization

In this method, the particle is formed by evaporation of the solvent from the matrix material. However, the solidification of the matrix also can be caused by a chemical change in a number of processes; a core material is dissolved in a polymeric matrix during formation of the particles. A simple example of this kind is actually Spray drying method, in which the particle is formed by evaporation of the solvent from the matrix material. However the chemical change can also cause solidification of materials.

1.13. Release kinetics patterns of microspheres

Although, the aim of the microsphere is to protect the core by surrounding wall. The wall may get ruptured at the time of usage. microsphere contents may get ruptured by melting the wall, dissolving it under particular conditions , as in the case of an enteric coating , in other system it get ruptured by solvent action , enzyme action.

Microsphere can be used to slow the release of a drug into the body. This may help for the controlled release dose to substitute for several doses of non-encapsulated drug and also may decrease toxic side effects for some drugs by preventing high initial concentrations in the blood.

1.14. Applications of microspheres (N. K. Jain 2009)

1. Microspheres in vaccine delivery.
2. Targeting using microparticulate carriers
    a. Targeting may be provided by:
    b. By controlling the size of the microspheres
    c. By conjugation with antibodies
    d. By incorporation of magnet particle
3. Monoclonal antibodies mediated microspheres targeting
4. Chemoembolisation
5. Imaging
6. Topical porous microspheres
7. Surface modified microspheres

AIM AND OBJECTIVE

2. AIM AND OBJECTIVE

Atypical antipsychotic Quetiapine was approved by the US food and drug administration (FDA) used for the treatment of schizophrenia is a severe illness with substantial effects on individual and social functioning, Quetiapine and its active metabolite N-desalkyl-Quetiapine have affinities to dopaminergic D1-and D2receptors, 5-HT2 receptors. It is used orally for the treatment of schizophrenia and has a low bioavailability of 9%, because of its poor absorption in lower gastro intestinal tract. It undergoes little or no hepatic metabolism and its elimination half life is 6 hrs.

- Quetiapine (seroquel) is available as tablets for oral administration, containing 50 mg, 100 mg, 200 mg, 300 mg, or 400mg of Quetiapine.
- The once daily dosing of Quetiapine reaches similar overall plasma concentrations to the twice daily dosing of immediate release.
- Overview the clinical efficacy of 20 trials have been completed to determine Quetiapine in total 3,231 patients have been recruited; 1,677 of these patients were diagnosed with schizophrenia, 951 patients took part in short term trials over six weeks .
- Switching from Quetiapine immediate release or other antipsychotics to Quetiapine microspheres was feasible in a short time and maintained effective treatment.

Sustained release or controlled release of formulation can be attempted as:

- ✓ Microsphere's will provide the sustained release and to reduce the dose dependent side effects as well as to improve patient compliance.
- ✓ Sustained release and controlled release tablets by using Hydrophilic Matrices to retard and control the rate of drug release.
- ✓ Liposome drug delivery is to reduce hepatic toxicity enhanced cellular uptake and alters pharmacokinetics.
- ✓ Microspheres for the controlled release of various drugs.

Objectives:

The development of efficient orally delivered mucoadhesive drug delivery system includes advantages like:

- Maximized absorption rate is mainly due to intimate contact of drug with the mucus membrane to improve and enhance bioavailability of drugs.
- Drug protection is improved by polymer encapsulation and longer gut transit time is obtained, resulting in extended periods for absorption.
- Multiple dosing is avoided and thereby counteracts the side effects.
- The main objective is mainly to develop alginate mucoadhesive microspheres of Quetiapine by orifice-ionic gelation process using mucoadhesive polymers release of the drug for extended period of time.
- Formulate and evaluate the microspheres of Quetiapine.
- To study the effect of different polymers and different ratios of polymers employed.
- Performing the stability studies as per ICH guidelines.

PLAN OF WORK

3. PLAN OF WORK

- **LITERATURE REVIEW**
- **SELECTION OF DRUG, POLYMER AND EXCIPIENTS**
- **PROCUREMENT OF DRUG, POLYMER AND EXCIPIENTS**
- **EXPERIMENTAL WORK**

A) PREFORMULATION STUDY

- **Identification of drug**
  - By FTIR spectroscopy
  - By melting point
- **Physicochemical parameters**
  - Organoleptic properties
  - Solubility profile
- **Analytical methods**
  - Determination of λ_{max}
  - Development of standard curve of Quetiapine fumarate
  - Determination of percentage purity of drug
- **Determination of compatibility for drug with polymer**
  - By FTIR spectroscopy
  - By DSC thermal analysis

B) EVALUATION OF MUCOADHESIVE MICROSPHERES

- Percentage yield
- Particle Size analysis
- Drug content estimation and Encapsulation efficiency
- Percentage moisture content
- Scanning electron microscopy
- *In -vitro* wash - off test for mucoadhesion
- *In -vitro* drug release studies

C) KINETIC STUDIES

D) STABILITY STUDIES

- **RESULTS AND DISCUSSION**
- **SUMMARY AND CONCLUSION**
- **FUTURE PROSPECTS**
- **BIBLIOGRAPHY**

LITERATURE REVIEW

4. LITERATURE REVIEW

Literature review indicating advancement in Microsphere drug delivery system is given by:

Senthil A., et al., (2011) were prepared by glipizide microspheres containing chitosan simple emulsification phase separation technique using glutaraldehyde as a cross-linking agent. Microspheres were discrete, spherical, and free flowing. The microspheres exhibited good mucoadhesive property in the in vitro wash-off test and also showed high percentage drug entrapment efficiency. A 3^2 full factorial design was employed to study the effect of independent variables, polymer-to-drug ratio (X1), and stirring speed (X2) on dependent variables percentage mucoadhesion, t80, drug entrapment efficiency, and swelling index. Percentage mucoadhesion after 1 hour was 78%. The drug release was also sustained for more than 12 hours.

Ofokansi KC., et al., (2007) had formulated ceftriaxone sodium-loaded mucoadhesive microspheres by the emulsification cross-linking method using arachis oil as the continuous phase. The release profile of ceftriaxone sodium from the microspheres was evaluated in both simulated gastric fluid (SGF) without pepsin (pH 1.2) and simulated intestinal fluid (SIF) without pancreatin (pH 7.4). Release of microspheres by diffusion following non-Fickian transport mechanism and was higher and more rapid in SIF than in SGF. The results obtained from this study may indicate that ceftriaxone sodium could be successfully delivered rectally when embedded in microspheres formulated with either type a gelatin alone or its admixtures with porcine mucin.

Dhamane Aligave H., et al., (2011) had formulated and evaluated the potential use of mucoadhesive Carbopol 934P microspheres for gastroretentive delivery of Cefuroxime Axetil. Microspheres were prepared by spray drying technique using 3^2 full factorial designs. The formulated Microspheres were characterised for Mucoadhesion time, Encapsulation Efficiency, Particle size analysis, DSC, XRD, IR and In-vitro drug release. The result of mucoadhesion study shows better retention (320±15 min) of formulation in upper part of GIT. The release of the drug was prolonged up to 10hrs (96.46±0.76).

Shee Dutta Maurya., et al., (2010) had formulated and systemically evaluated of mucoadhesive propranolol hydrochloride microspheres for its potential use in the treatment of hypertension, myocardial infraction and cardiac arrhythmias. This containing carbopol-934P as mucoadhesive polymer and ethyl cellulose as carrier polymer, were prepared by an emulsion-solvent evaporation technique of time. A 3^2 full factorial design was employed to study the effect of independent variables, drug-to-polymer-to-polymer ratio the best batch exhibited a high drug entrapment efficiency of 54 %; 82% mucoadhesion after 1 h and particle size of 110 µm. A sustained pattern of drug release was obtained for more than 12 h.

Vijay Kumar Tilak., et al., (2010) were prepared repaglinide mucoadhesive microspheres by the emulsion solvent evaporation technique consisting of chitosan mucoadhesive, an oral hypoglycemic agent and Eudragit RS-100 as polymer. The microspheres were also evaluated for their microencapsulation efficiency, in vitro wash-off mucoadhesion test, in vitro drug release and in vivo study. All the formulations were

followed by Matrix-Peppas model. The drug release was also found to be slow and extended for 24 h.

Madhavi Boddupalli B., et al., (2010) *was* to formulated and evaluated mucoadhesive microsphers of Venlafaxine Hydrochloride by using carbopol and HPMC K4M as mucoadhesive polymers. There was sustained release up to 12 hours and almost 70% of mucoadhesion was observed after 12 hours. The results were encouraging and further studies are required for in-vivo efficiency.

Okore VC., et al., (2010) were successfully prepared by emulsification-internal gelation technique with a maximum incorporation efficiency of 93.29 ± 0.26%. The *in vitro* wash-off test indicated that the microspheres had good mucoadhesive properties. The wash-off was faster at simulated intestinal fluid (phosphate buffer, pH 7.4). The *in vitro* drug release mechanism was non-fickian type controlled by swelling and relaxation of polymer. There was no significant change in drug content and cumulative drug release of drug-loaded microspheres stored at different storage condition after 8 weeks of study.

Rajeshwarkant R., et al., (2010) had characterized of mucoadhesive microspheres with Famotidine as model drug for prolongation of gastric residence time Using mucoadhesive polymers sodium CMC and sodium alginate. *In vitro* drug release studies were performed and drug release evaluated. The prepared microspheres exhibited prolonged drug release (8h). The *In vitro* studies demonstrated diffusion-controlled drug release from the microspheres.

Shiv Shankar Hardenia., et al., (2011) were prepared and evaluated ethylcellulose microspheres containing ciprofloxacin for in-vitro performance of ciprofloxacin. Ciprofloxacin microspheres containing ethylcellulose were prepared by

emulsion solvent diffusion evaporation method. The best cumulative release was achieved after 24 hrs i.e. 91.6%. The Mucoadhesive property of the ethylcellulose microspheres was evaluated by in-vitro wash off test. The microspheres exhibited 75% mucoadhesion and showed good drug entrapment efficiency. By, above results it was concluded that ethylcellulose microspheres showed reproducible results, with good Mucoadhesive properties and good surface morphology.

Nagda Chirag., et al., (2009) were designed, characterized and evaluated bioadhesive microspheres of ACE employing polycarbophil as bioadhesive polymer. Bioadhesive microspheres of ACE were prepared by double emulsion solvent evaporation method. The *in-vitro* release studies were performed using pH 6.8 phosphate buffer. The drug loaded microspheres in a ratio of 1:5 showed 38 % of drug entrapment, percentage mucoadhesion was 79 % and 89 % release in 10 h. The in vitro release profiles from microspheres of different polymer-drug ratios followed Higuchi model.

Ram Chand Dhakar., et al., (2010) were prepared and evaluated by emulsification solvent evaporation method using Sodium carboxy methyl cellulose (SCMC), Carbopol 934P (CP), and Hydroxyl propyl methyl cellulose K4M (HPMC) as a mucoadhesive polymers. Microspheres prepared were found discrete, spherical and free flowing. Among all the formulation, formulation F1 containing SCMC and F2 containing CP showed the best reproducible results and mucoadhesive profile with good surface morphology.

Nalanda Rangari T., et al., (2010) was to formulated and systematically evaluated in vitro performance of mucoadhesive microsphere of Pioglitazone HCL. Pioglitazone HCL mucoadhesive microsphere were prepared from Orifice Ionic Gelation

Method using variouspolymers viz, Sodium Alginate, Carbopol 934 P, Carbopol 971 P NF, Carbopol 974 P NF,HPMC K 100 M and Polycarbophil in different proportion. The best batch exhibited a high drug entrapment efficiency of 65% and a swelling index of 1.21 percentage mucoadhesion after 1 hour was 78%. The drug release was also sustained for more than 12 hours.

Mahendra Singh., et al., (2011) had prepared by emulsion cross linking method using Glutaradehyde as a cross linking agent. Gelatin A and Chitosan were used as polymer and co polymer respectively. All the prepared microspheres were evaluated for physical characteristics, such as particle size, incorporation efficiency, swelling index, *in vitro* bioadhesion using rat jejunum and *in vitro* drug release in pH 6.6 phosphate buffer. The data indicates the verapamil hydrochloride release followed Higuchi's matrix and Peppas model. Stability studies showed stability of formulation at all the conditions to which the formulations were subjected.

Venkateswaramurthy N., et al., (2011) was to designed and characterized mucoadhesive microspheres containing Clarithromycin as an anti-*H. pylori* agent to deliver the drug specifically to mucus layer where *H.pylori* resides and evaluate the effectiveness of the mucoadhesive microspheres for *H. pylori* eradication therapy. Microspheres were prepared by using Eudragit RL100 as matrix and Carbopol 974P as a mucoadhesive polymer. The microspheres were prepared by emulsion solvent evaporation technique. The prepared microspheres were evaluated with respect to the particle size, production yield, encapsulation efficiency, shape and surface properties, mucoadhesive property, *in vitro* drug release and suitability for anti *Helicobactorpylori* effect.

Jhbhatt., et al., (2009) were prepared Metronidazole Microsphere employing sodium alginate in combination with four mucoadhesive polymers – sodium CMC, Methylcellulose, Carbopol and HPMC-K4M as coat materials with different polymers ratios. The microspheres were found to discrete, spherical, free flowing, and of the monolithic matrix type. The mucoadhesive microspheres were evaluated by in vitro and in vivo methods using Gamma Scintigraphy for controlled release.

Venkateswaramurthy S., et al., (2010) had formulated and systematically evaluated *in vitro* performances of Furazolidone mucoadhesive microspheres were prepared by simple emulsification phase separation technique using Eudragit RS100 as matrix and Carbopol 974P and Hydroxy propyl methyl cellulose K4M as mucoadhesive polymer. The prepared microspheres were evaluated with respect to the particle size, encapsulation efficiency, shape and surface properties, mucoadhesive property, *in vitro* drug release and suitability for anti *Helicobacter pylori* effect. The best batch exhibited a high drug entrapment efficiency of 82.12 % and percentage mucoadhesion after 1 h was 93.35 %. The drug release was also sustained up to 12 h.

Nishanth Kumar N., et al., (2011) was formulated and evaluated gliclazide mucoadhesive microsphere using hydroxypropylmethylcellulose K4M and carboxymethylcellulose as polymers were prepared by simple emulsification phase separation technique using glutaraldehyde as across-linking agent. Twenty preliminary trial batches, F1 to F20 batches of microspheres were prepared by using different volume of cross-linking agent, cross-linking time and 3:1 polymer-to-drug ratio. Among the two polymers, the best batch was hydroxypropylmethylcellulose K4M exhibited a high drug

entrapment efficiency of 69% and a swelling index1.16 % mucoadhesive after 1hour was 70% and the drug release was also sustained for more than 10 h.

Saravanakumar K., et al., (2011) were formulated and developed of naproxen sodium microsphere two investigated factors (independent variables) were the stabilizer agent concentration in the aqueous phase (%w/v PVA) and the polymer concentration in the organic phase (%w/v HPMC K15M).The results showed that encapsulation efficiency was significantly affected by the two investigated factors, with PVA concentration having a highly negative effect, probably due to naproxen sodium's solubility enhancement in the aqueous phase in the presence of higher amounts of stabilizer. These results demonstrate hat it is possible to control the quantity of drug loaded in the microspheres.

Dasai Sapna., et al., (2010) had formulated and systematically evaluated the performances of mucoadhesive microspheres of midazolam containing carbopol 934P were prepared by emulsion cross linking technique using glutaraldehyde as a cross-linking agent. Results of preliminary trials indicate that volume of cross-linking agent, time for cross-linking, polymerto- drug ratio and speed of rotation affected characteristics of microspheres. The best batch exhibited a high drug entrapment efficiency of 93% and a swelling index of 1.11% and *in vitro* bioadhesion was 89%. The drug release was also sustained for 12 h.

Malay Das K., et al., (2008) were developed of diltiazem-loaded mucoadhesive microspheres successfully prepared by emulsification-internal gelation technique using different polymers. The scanning electron microscopic study indicated that the microspheres were spherical in shape. The *in vitro* wash-off test indicated that the microspheres had good mucoadhesive properties. The wash-off was faster at simulated

intestinal fluid (phosphate buffer, pH 7.4) than that at simulated gastric fluid (0.1 M HCl, pH 1.2). The *in vitro* drug release mechanism was non-fickian type controlled by swelling and relaxation of polymer.

Veena Belgamwar., et al., (2009) was to prepared and evaluated mucoadhesive multiparticulate system for oral drug delivery using ionic gelation technique. Microspheres composed of various mucoadhesive polymers including HPMC of various grades like K4M, K15M, K100M, E50LV, Carbopol of grades 971P, 974P and polycarbophil were prepared. In this technique cross linking of sodium alginate with calcium chloride was done which retarded the release of drug from the mucoadhesive polymer. Metoprolol release from the multiparticulate system was regulated and extended until 12 hours and exhibited a non fickian drug release kinetics approaching to zero order, as evident from the release rate exponent values which varied between 0.57 to 0.73. The stability studies performed on the optimized batches at 40°C / 75% RH for 90 days.

Hamouda AO., et al., (2010) were developed controlled release amoxicillin trihydrate (MOX) and Chitosan, a cationic polymer was selected as and sodium carboxymethyl cellulose (Na CMC), an anionic polymer was selected for mucoadhesion and sustained release respectively. The preparation of microspheres was carried out using ionic gelation method. Release profile followed zero order kinetic with around 20 % constant drug release per hour up to 5 h. Therefore, it is safely concluded that mucoadhesive controlled release microspheres of amoxicillin were successfully developed and can be used for optimum delivery of MOX either for local gastric infections or for systemic drug delivery.

Yadav S., et al., (2011) had to formulate and evaluated sustained release mucoadhesive microspheres of Acyclovir loader Sodiumcarboxymethylcellulose and hydrxypropylmethylcellulose were used as mucoadhesive polymers. The microspheres were prepared using solvent evaporation technique. The results of mucoadhesion study showed better retention of Sodium CMC microspheres (8.0±0.8 h) in duodenal and jejunum regions of intestine. Overall, the result indicated prolonged delivery with significant improvement in oral bioavailability of acyclovir from mucoadhesive microspheres due to enhanced retention in the upper GI tract.

Literature review indicating work carried out on selected drug, quetiapine fumarate is given below:

Deepak Sahu., et al., (2010) was developed sustained release matrix tablets of quetiapine fumarate using different polymers viz. Hydroxy propyl methyl cellulose (HPMC) and PVP K30. After evaluation of physical properties of tablet, the in vitro release study was performed in 0.1 N HCl, pH 1.2 for 2 h and in phosphate buffer pH 6.8 up to 12 h. Dissolution data was analyzed by Higuchi expression. Among all the formulations, formulation QFSRT/08 which contains 60% HPMC K15M and 06% of PVP K30 release the drug which follow Higuchi kinetics via, swelling, diffusion and erosion and the release profile of formulation QFSRT/08 was comparable with the prepared batch products. Stability studies (40±2ºC/75±5%RH) for 6 months indicated that quetiapine fumarate was stable in the matrix tablets.

Jaydeep Patel., et al., (2010) were prepared sustained release microspheres of the anti-psychotic drug, quetiapine fumarate, using ethyl cellulose as the polymer and utilizing emulsion solvent evaporation and extraction technique. A 3^2 factorial factorial

design was applied to investigate the influence of drug: polymer ratio and average particle size on release characteristics. The optimized batch showed no signs of interaction with sustaining the drug release up to 12 h along with identical release behavior to that of marketed sustained release tablet.

*P**attanyak Durga., et al., (2011)*** had prepared and characterized sustained release matrix tablets of quetiapine fumarate using different polymers viz., Hydroxy propyl methyl cellulose (HPMC) and PVP K30. After evaluation of physical properties of tablet, the in vitro release study was performed in 0.1 N HCl, pH 1.2 for 2 h and in phosphate buffer pH 6.8 up to 12 h. The effect of polymer concentration and polymer blend concentration were studied. Dissolution data was analyzed by Higuchi expression. Among all the formulations, formulation QFSRT/08 which contains 60% HPMC K15Mand 06% of PVP K30 release the drug which follow Higuchi kinetics via, swelling, diffusion anderosion and the release profile of formulation. Stability studies (40±2ºC/75±5%RH) for 6 months indicated that quetiapine fumarate was stable in the matrix tablets.

Haresh T Mulani., et al., (2011) was selected as a model drug for our present investigation. Quetiapine shows pH dependent solubility, using Eudragit L30 D55, Sodium alginate and HPMC was used as retarding and matrix forming agent respectively. The prepared granules and tablets were characterized for its pharmaceutical properties, drug release studies and release kinetics. The ratio of HPMC and sodium alginate was studied and found suitable in ratio of 1:1, 1: 1.5, and 1.5:1 when used with 10 % acidifying and granulating agent to achieve not only desired release profile but also for better pharmaceutical standards.

Kiran Kumar M., et al., (2010) were to overcome this problem by utilizing Succinic acid as pH adjuster and to achieve pH-independent release from matrix and coated tablets. Eudragit-RSPO was used as matrix former and Eudragit-RSPO & RLPO mixture was employed for coating of tablets. Drug release from tablets was studied in pH 1.2 and 6.8 buffers. Effect of addition of Succinic acid on drug release and drug: Succinic acid ratio on drug release was studied. The release of Quetiapine Fumarate from Eudragit- RLPO and RSPO coated tablets was found to be constant and more pH-independent than matrix tablets containing Eudragit RSPO.

Ram Chand Dhakar., *et al.*, (2008) had to formulate and evaluate mucoadhesive microspheres of rosiglitazone maleate were prepared by emulsification solvent evaporation techniques. Microspheres were found discrete, spherical and free flowing. Among all the formulations containing carbopol 934 showed good mucoadhesive property.the work has demonstrated that among all the formulations of microspheres, particularly formulation F1 are promising candidates for the sustained release in gastrointestinal tract.

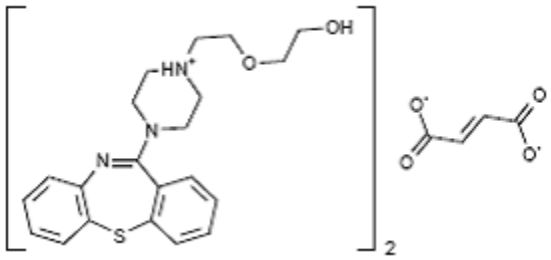
DRUG AND EXCIPIENTS PROFILE

5. DRUG AND EXCIPIENTS PROFILE

5.1: Drug profile

(www.rxlist.com/cgi/generic 2/quetiapine)

Quetiapine is an antipsychotic drug (Merck index, 1998)



Molecular Formula	:	$(C_{21}\ H_{25}N_3O_2S)\ 2.\ C_4H_4O_4$
Chemical Name	:	2-[2-(4-dibenzo {b,f)[1,4] thiazepin-11-yl-1-iperazinyl) ethoxy] Fumarate.
Molecular Weight	:	883.11dalton
Melting Point	:	172 - 174°C
Synonyms	:	seriqyek
Physical State	:	white to off – white crystalline powder
Solubility	:	slightly soluble in water and soluble in methanol.

Clinical pharmacology

Pharmacodynamics (or) Mechanism of action

Seroquel is an antagonist at multiple neurotransmitter receptors in the brain. Seroquel is an antagonist at $5HT_{IA}$ and $5HT_2$, dopamine D_1 and D_2 histamine H_1 and at adrenergic α_1 and α_2 receptors.

Seroquel has not appreciable affinity at cholinergic muscarnic and benzodiazinereceptgors. Seroquel's antagonism of histamine H1 receptors may explain the somnolence observed with this drug. Seroquel's antagonism of adrenergic α_1 receptors may explain the orthostatic hypotension.

Pharmacokinetics: (Goodman and Gilman's., 2006)

Parameters		**values**
Availability of oral	:	9%
Urinary excretions	:	<1%
Bound in plasma	:	83%
Clearance	:	$19 ml min^{-1.} Kg^{-1}$
Volume of distributions	:	10±4liters/kg
Half life	:	1-6 hours
Peaktime	:	1-1.8 hours
Peak concentrations	:	278 ng/ml

The multiple dose pharmacokinetics of quetiapine is dose proportional within the proposed clinical dose range and quetiapine accumulation is predictable upon multiple dosing.

Absorption

Quetiapinefumarate is rapidly absorbed after oral administration, reacting peak plasma concentration in 1.5 hours. The tablet forumulation is 100% bioavilabile relative to solution.

Distribution

Quetiapine is widely distributed throughout the body. It is 83% bound to plasma proteins at therapeutic concentration.

Metabolism

Quetiapine is extensively metabolized by the liver.The major metabolic pathways are sulfoxidation to the sulfoxable metabolite and oxidation to the parent acid metabolite.

Elimination

Following a single oral dose of 14° C – quetiapine, less than 1% of the administrated dose was excreted as unchanges drug. Approximately 73% and 20% was recovered in the urine and focus respectively.

Population subgroups

Age – oral clearance of quetiapine was reduced by 40% in elderly patients compared to young patients.

Gender: there is no gender effect o the pharmacokinetics of quetiapine

Race: there is no gender effect on the pharmacokinetics

Smoking – smoking has no effect on the oral clearance of quetiapine

Indications and usage

Bipolar mania

Seroquer is indicated for thetreatment of acutemanic episodes associated with bipolar disorder, as either monotherapy or adjuct therapy to lithium (or) diralproex. Schizophrenia, Seoquer is indicated for the treatment of schizophrenia

Dosage and administration

Bipolar mania

Seroquer should be intiated in bipolar manic patients with 100mg BID dose on first day, followed by an increment dose of 100mg/day uptoan maximum intake of 800mg/day.

Schizophrenia

Seroquer should be initiated in schizophrenic patients with 250mg BID dose on first day, followed by an increment dose of 25 to 50mg/day maximum intake of 300 to 400mg/day, either in BID to TID.

Adverse effects

The most frequent adverse effects with quetiapinehas been somnolence. Other adverse effects have included mild asthemia, anxiety, dizziness, myalgia, rhinithis,

dyspepsia and rises in plasma triglyceride levels. There have been rare reports of priapism (or) peripheral oedema.

Drug abuse and dependence

Clinical trials did not reveal any tendency for any drug seeking behavior of the drug quetiapinefumarate.

Drug Interactions: Quetiapine is metabolized in the liver with the help of CYP 3A4 Isoenzyrnes. Ouetlapine does not inhibit any of the CYP 450 isoenzymes nor does it appear to induce the CYP $3A_4$Isoenzymes, because of these properties it is unlikely to affect metabolism of drugs mediated through CYP 450 enzymes. However drugs that alter the activity of CYP $3A_4$isoenzymes have the potential for drug interactions with quetiapine.

Table 5.1: Common drug interaction with Quetiapine

S.No	Interacting Drug	Effect of Interaction
1.	Carbamazepine	May increase metabolism level
2.	Erythromycin, Clarithromycin	Possible decrease metabolism, increase side effects
3.	Fluvoxamine	Possible decrease metabolism, increase side effects
4.	Ketoconazole, Itraconazole, fluconazole, Verapamil, diltiazem	Possible decrease metabolism, increased levels, side effects
5.	Nefazodone	Possible decrease metabolism,

		increased levels, side effects
6.	Phenyotin	Increased Quetiapine clearance, decreased levels
7.	Thioridazine	May Increase Quetiapine clearance level.
8.	Diazepam and alcohol	Causes orthostatic hypotention
9.	Alprazolam	Causes orthostatic hypotention
10.	Terazosin	Causes orthostatic hypotention

Overdosage

Hypotension tachycardia and somnolence were the main clinical events observed in quetiapine overdosage. A symptomatic prolongation of the AT interval was also observed on quetiapine overdosage.

Contraindications:

Seroquer is contraindicated in individuals with a known hypersensitivity to this mediation (or) any of its ingredients.

Precautions

In USA it is recommended the patients should have an eye examination to detect cataract formation before starting therapy with quetiapine and every 6 months during treatment.

Patient information

- Patients should be advised not to breast feed if they are taking seroquel.
- Patients should be advised to notify their physician if they become pregnant (or) intend to become pregnant during therapy.
- Patients should be advised to avoid consuming alcoholic beverages white taking seroquel.
- Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

Dosage

Initially 25mg bid, increase 50 to bid, usual dose range 300 – 450mg daily max; 750mg/dayelderly initially, 25mg daily.

TRADE NAMES

SEROQUEL

- Tablets25mg.
- Tablets100mg.
- Tablets 400mg.

SEROQUEL XR

- ❖ Tablets 50mg, 100mg, 200mg, and 400mg.

Disease profile

Schizophrenia is a common and serious mental disorder in which majority of patients require long - term antipsychotic treatment.Despite the availability of effective antipsychotics, functional outcome in schizophrenic patients has not changed significantly over the past century. They may be -related to the fact that while first generation drugs improves positive symptoms of schizophrenia in the majority of patients, they have little impact an negative symptoms or neurocognitive functionQuetiapine is a new atypical dibenzothiazepine antipsychotic introduced that is expected to fulfil the main goals in treatment of schizophrenia. Above these, it has effect on affective symptoms for difficult cases of schizoaffective disorders, depression with psychosis and other mixed conditions.Quetiapine is very well tolerated, with no requirement for routine anti parkinsonian drugs. It is safe for heart with no requirement for routine ECG and blood monitoring. It is the only first line antipsychotic with placebo level Extra Pyramidal Side effects as reported by number of studies.

5.2: POLYMERPROFILE

5.2.1:SODIUM ALGINATE *(Raymond C., et al.,2003)*

- **Nonproprietary Names**

  BP : Sodium alginate,

  PhEur : Natriialginas,

  USPNF : Sodium alginate

- **Synonyms**

  Algin; alginic acid, sodium salt; E401; Kelcosol; Keltone; Protanal; sodium polymannuronate.

- **Chemical Name and CAS Registry Number**

  Sodium alginate [9005-38-3]

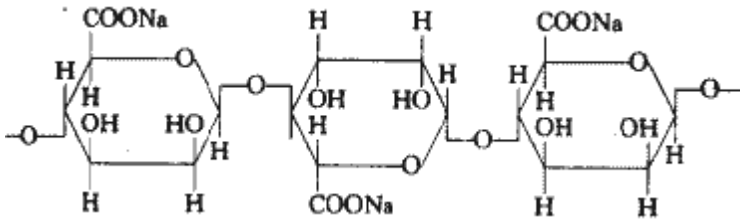
- **Empirical Formula**

  $(C_6H_7O_6Na)_n$

- **Molecular Weight**

  The block structure and molecular weight of sodium alginate samples has been investigated.

- **Structural Formula**



- **Functional Category**

  It has stabilizing agent; suspending agent; tablet and capsule disintegrant; tablet binder; viscosity-increasing agent.

- **Grades**

  Various grades of sodium alginate are available yielding aqueous solutions of varying viscosities within a range of 20 to 400 centipoises in 1% solution at 20 °C.

- **Applications in Pharmaceutical Formulation or Technology**

  Sodium alginate is used for oral and topical pharmaceutical formulations.

  - In tablet formulations, sodium alginate may be used as both a binder and disintegrant,diluents in capsule formulations. Sustained release oral formulations are prepared by using, since it can delay the dissolution of a drug from tablets,

capsules and aqueous suspensions. In topical formulations, sodium alginate is mainly used as a thickening and suspending agent in product such as variety of pastes, creams, and gels, and as a stabilizing agent for oil-in-water emulsions

- Recently, sodium alginate has been used mostly for microencapsulation of drugs,contrastwith the more conventional microencapsulation techniques which use organic-solvent systems. It has also been used in the formulation of nanoparticles. Other NDDS containing sodium alginate include ophthalmic solutions that form a gel in situ when administered to the eye.

- **Description**

Sodium alginate occurs naturally as an odorless and tasteless, white to pale yellowish-brown colored powder.

- **Typical Properties**

Acidity/alkalinity: pH 7.2 for a 1% w/v aqueous solution

- **Solubility**

Practically insoluble in ethanol (95%), ether, chloroform, and ethanol/water mixtures in which the ethanol content is greater than 30%. Also, the pH is less than 3. It is slowly soluble in water, forming a viscous colloidal solution.

- **Stability and Storage Conditions**

Sodium alginate is a hygroscopic material, although it is stable if stored at low relative humanities and a cool temperature.

5.2.2: CARBOMER *(Raymond C. Rowe, 2003)*

1. Nonproprietary Names

- **BP** :Carbomers
- **PhEur :**Carbomera
- **USPNF** :Carbomer

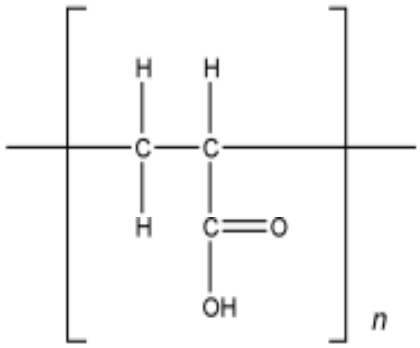
2. Synonyms

Acritamer; acrylic acid polymer; Carbopol; Carboxypolymethylene, polyacrylic acid; carboxyvinyl polymer; Pemulen; Ultrez

3. Chemical Name and CAS Registry Number: Carbomer [9003-01-4]

4. Molecular Weight: 86,000

5. Structural Formula



Acrylic acid monomer unit in carbomer resins.

Carbomer polymers are formed from repeating units of acrylic acid. The monomer unit is shown above. The polymer chains are crosslinked with allyl sucrose or allylpentaerythritol.

6. Functional Category

Bioadhesive; emulsifying agent; release-modifying agent; suspending agent; tablet binder; viscosity-increasing agent

7. Applications in Pharmaceutical Formulation or Technology

Carbomers are mainly used in liquid or semisolid pharmaceutical formulations as suspending or viscosity-increasing agents. Formulations include creams, gels, and ointments for use in ophthalmic, rectal, and topical preparations. Carbomer grades, even with low residual benzene content, such as carbomer 934P, are no longer included in the PhEur 2005. Carbomer having low residuals only of ethyl acetate, such as carbomer 971P or 974P, may be used in oral preparations, in suspensions, tablets, or sustained release tablet formulations. In tablet formulations, carbomers are used as dry or wet binders and as a rate controlling excipient. In wet granulation processes, water or an alcohol–water blend is used as the granulating fluid. Anhydrous organic solvents have also been used, with the inclusion of a polymeric binder. The tackiness of the wet mass can be reduced with the addition of certain cationic species to the granulating fluid or, in the case of water, with talc in the formulation.

Table 5.2: Uses of carbopol 974P

Uses	Concentration (%)
Emulsifying agent	0.1–0.5
Gelling agent	0.5–2.0
Suspending agent	0.5–1.0
Tablet binder	5.0–10.0

8. Description

Carbomers are white-colored, 'fluffy', acidic, hygroscopic powders with a slight characteristic odour.

9. Typical Properties

- **Acidity/alkalinity** : pH = 2.7–3.5 for a 0.5% w/v aqueous dispersion

pH = 2.5–3.0 for a 1% w/v aqueous dispersion

- **Density (bulk)** :1.76–2.08 g/cm^3
- **Density (tapped)** :1.4 g/cm^3
- **Melting Point** : Decomposition occurs within 30 minutes at 260°C
- **Moisture Content**

Normal water content is up to 2% w/w. However, carbomers are hygroscopic and typicalequilibrium moisture content at 25°C and 50% relative humidity is 8–10%

w/w. Themoisture content of a carbomer does not affect its thickening efficiency, but an increase inthe moisture content makes the carbomer more difficult to handle because it is less readilydispersed.

❖ **Solubility**

It is soluble in water and after neutralization in ethanol (95%) and glycerin.Although they are described as 'soluble', carbomers do not dissolve but merely swell to aremarkable extent, since they are three-dimensionally crosslinked micro gels. Furthermore,the pharmacopeia specifications are unclear, in that neutralization with long-chain aliphaticamines or ethoxylated long-chain amines is required for swell ability in ethanol, and withwater-soluble amines for swell ability in glycerin.

❖ **Viscosity (dynamic)**

Carbomers disperse in water to form acidic colloidal dispersions of low viscosity that, whenneutralized, produce highly viscous gels. Carbomer powders should first be dispersed intovigorously stirred water, taking care to avoid the formation of indispersible lumps, then neutralized by the addition of a base. The Carbopol ETD and Ultrez 10 series of Carbomers was introduced to overcome some of the problems of dispersing the powder into aqueous solvents. These carbomer resins wet quickly yet hydrate slowly, while possessing a lowerunneutralized dispersion viscosity.

10. Stability and Storage Conditions

Carbomers are stable, hygroscopic materials that may be heated at temperatures below 104°C for up to 2 hours without affecting their thickening efficiency.

However, exposure to excessive temperatures can result in discoloration and reduced stability.

5.2.3. HYPROMELLOSE (HYDROXYPROPYL METHYLCELLULOSE)

(Rowe C. 2003)

1. Nonproprietary Names

- **BP :** Hypromellose
- **JP :** Hydroxypropylmethylcellulose
- **PhEur :** Hypromellosum
- **USP :** Hypromellose

2. Synonyms

Benecel MHPC; E464; hydroxypropyl methylcellulose; HPMC; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; Metolose; Tylopur.

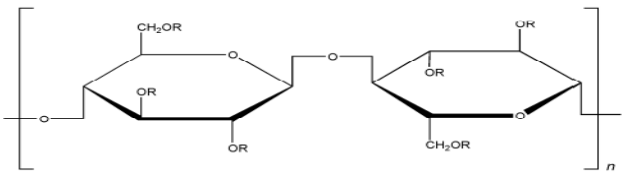
3. Chemical Name and CAS Registry Number

Cellulose hydroxypropyl methyl ether [9004-65-3]

4. Molecular Weight

10,000 – 1,500,000.

5. Structural Formula



Where R is H, CH_3, or CH_3CH (OH) CH_2

6. Functional Category

Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

7. Applications in Pharmaceutical Formulation or Technology

Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations. In oral products, hypromellose is primarily used as a tablet binder, in film-coating, and as matrix for use in extended-release tablet formulations. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules. Depending upon the viscosity grade, concentrations of 2-20% w/w are used for film-forming solutions to film-coat tablets. Hypromellose at concentrations 0.45-1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions. Lower-viscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents.

8. Description

Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder.

9. Typical Properties

- **Acidity/alkalinity** : pH = 5.5–8.0 for a 1% w/w aqueous solution.
- **Density (bulk)** : 0.341 g/cm^3
- **Density (tapped)** : 0.557 g/cm^3
- **Density (true)** : 1.326 g/cm^3
- **Melting Point** : browns at 190 – 200°C; chars at 225 – 230°C

  Glass transition temperature is 170 - 180^{o} C

Table 5.3: Various grades of hypromellose

Methocelproduct	USP 28 designation	Nominal viscosity (mPa s)
Methocel K100 Premium LVEP	2208	100
Methocel K4M Premium	2208	4000
Methocel K15M Premium	2208	15 000
Methocel K100M Premium	2208	100 000
Methocel E4M Premium	2910	4000
Methocel F50 Premium	2906	50
Methocel E10M Premium CR	2906	10 000
Methocel E3 Premium LV	2906	3
Methocel E6 Premium LV	2906	6
Methocel E15 Premium LV	2906	15
Metolose 60SH	2910	50, 4000, 10 000
Metolose 65SH	2906	50, 400, 1500, 4000
Metolose 90SH	2208	100, 400, 4000, 15 000

❖ **Solubility**

It is soluble in cold water and forming a viscous colloidal solution, practically insoluble inchloroform, ethanol (95%) and ether. But it was soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane and mixtures of water andalcohol.

❖ **Viscosity (dynamic)**

A wide range of viscosity types are commercially available. Aqueous solutions are mostcommonly prepared, although hypromellose may also be dissolved in aqueous alcohols suchas ethanol and propan-2-ol provided the alcohol content is less than 50% w/w.

10. Stability and Storage Conditions

Hypromellose powder is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3–11. Increasing temperature reduces the viscosity of solutions. Hypromellose undergoes a reversible sol–gel transformation upon heating and cooling, respectively.

11. Incompatibilities

Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts.

MATERIALS AND EQUIPMENTS

6. MATERIALS AND EQUIPMENTS

6.1. LIST OF RAW MATERIALS

Table 6.1: List of Raw materials with the name of the Suppliers

S. No.	Name of Raw Material	Name of the suppliers
1	Quetiapine Fumarate	Astrazeneca Pharmaceutical Private Limited, Bangalore.
2	Sodium alginate(Low viscosity)	Qualigens Laboratories, Mumbai.
3	Hydroxy propyl methyl cellulose(K15M)	Paraschem suppliers, Pune.
4	Carbopol-974P	Paraschem suppliers, Pune.
5	Methanol	Qualigens Laboratories, Mumbai.
6	Calcium chloride	Qualigens Laboratories, Mumbai.
7	Ethanol (95%)	Qualigens Laboratories, Mumbai.
8	Potassium dihydrogen phosphate	SD fine – Chem. Limited, Mumbai
9	Sodium hydroxide	SD fine – Chem. Limited, Mumbai
10	Peteroleum ether	SD fine – Chem. Limited, Mumbai

6.2. LIST OF EQUIPMENTS

Table 6.2: List of Equipments with company name

S. No.	Name of the Equipments	Company
1	Electronic Balance	Shimadzu, BL-200H, Japan.
2	UV-Visible Spectrophotometer	Shimadzu, 1700, Japan.
3	FTIR Spectrophotometer	Shimadzu –S4008.
4	USP, Type II Dissolution Test Apparatus	Veego Scientifics, VDA-8DR, Mumbai.
5	USP Tablet Disintegrating apparatus	Veego Scientifics, VDA-8DR, Mumbai.
6	Differential Scanning Calorimeter	Schimadu DSC 60, Japan
7	Scanning Electron Microscopy(SEM)	SEM -3400 Hitachi, Mumbai
8	Digital pH Meter	Elico Scientifics-L1 610, Mumbai.
9	Hot air oven	Prescision Scientific co., P-1401, Chennai.
10	Humidity Chamber	Labtech, Ambala.
11	Melting Point Test Apparatus	Prescision Scientific co., Chennai.
12	Standard sieve	Jayant scientific, India.

EXPERIMENTAL WORK

7. EXPERIMENTAL WORK

7.1. PREFORMULATION STUDY

Before formulating a product, the physical and chemical properties of a drug substance have undergone some preformulation testing. It is the first step in rational development of dosage form.

7.1.1. Identification of drug

7.1.1. a) Identification by FTIR spectroscopy *(Skoog D.A., et al., 1996; IP,2007)*

Quetiapine fumarate discs were prepared by pressing the Quetiapine with potassium bromide and the spectra in between 4000 to 500 cm^{-1} was obtained under the operational conditions. The absorption maximums in spectrum obtained with the substance being examined correspond in position and relative intensity to those in the reference spectrum represented in Table 8.1 and shown in Figure 8.1.

7.1.1. b) Identificationby melting point *(Moffat., et al.,2004)*

Melting point of the drug was determined by capillary tube method.

7.1.2. Physicochemical parameters

7.1.2. a) Organoleptic properties *(Lachman L.,et al.,1991)*

The color, odor and taste of the drug were recorded using descriptive terminology.

7.1.2. b) Solubility study *(Moffat., et al.,2004)*

It is important to know about solubility characteristic of a drug in aqueous system, since they must possess some limited aqueous solubility to elicit a therapeutic response. The solubility of drug was recorded by using various descriptive terminologies. The solubility profile was represented in Table 8.2.

7.1.3. Analytical methods

7.1.3. a) Determination of λ max *(Swamy P.V., et al., 2007; USP,2009)*

The absorption maximum of the standard solution was scanned between 200-400 nm regions on UV-Visible spectrophotometer. The absorption maximum obtained with the substance being examined corresponds in position and relative intensity to those in the reference spectrum was shown in Figure 8.2.

7.1.3. b) Development of standard curve of Quetiapine *(IP,1996;USP,2009)*

Preparation of Phosphate buffer (pH 6.8)

Phosphate buffer (pH 6.8) was prepared according to I.P. 1996. Placed 50 ml of 0.2 M potassium dihydrogen phosphate in a 200 ml volumetric flask and 22.4 ml of 0.2M sodium hydroxide was added and volume was made upto required quantity with water.

Preparation of 0.2M Potassium dihydrogen phosphate

Dissolved 27.218 gm of potassium dihydrogen phosphate in water and made up to 1000 ml.

Preparation of stock solution of Quetiapine fumarate with pH 6.8

Accurately weighed 100 mg of Quetiapine, was dissolved in little quantity of pH 6.8 and volume was adjusted to 100 ml with the same to prepared standard solution having concentration of 30 µg/ml.

Procedure

From the stock solution, aliquots of 1, 2, 3, 4, 5 and 6 ml were transferred into 100 ml volumetric flasks and final volume was made upto 100 ml with pH 6.8. Absorbance values of these solutions were measured against blank (pH 6.8) at 293.5 nm

using UV-Visible spectrophotometer. The data was represented in Table 8.3, 8.4 and shown in Figure 8.3.

7.1.3. c) Determination of Percentage purity of Drug *(USP, 2009)*

Accurately weighed 100 mg of Quetiapine was dissolved in little quantity of methanol to get the concentration of 1mg/ml. The solution was pipetted out of about 0.5 ml to 3 ml and volume was made up with distilled water. From the above stock solution, the concentration and absorbance was observed. The absorbance was measured at 293.5 nm against the blank using by UV-Visible spectrophotometer. The percentage purity of drug was calculated by using calibration curve method (least square method). The data of percentage purity was represented in Table 8.5.

7.1.4. DRUG EXCIPIENT INTERACTION STUDIES

7.1.4. a) Determination of drug-polymer compatibility *(Aulton M.E.,et al.,2002)*

The proper design and formulation of a dosage form requires consideration of the physical, chemical and biological characteristics of all drug substances and excipients.

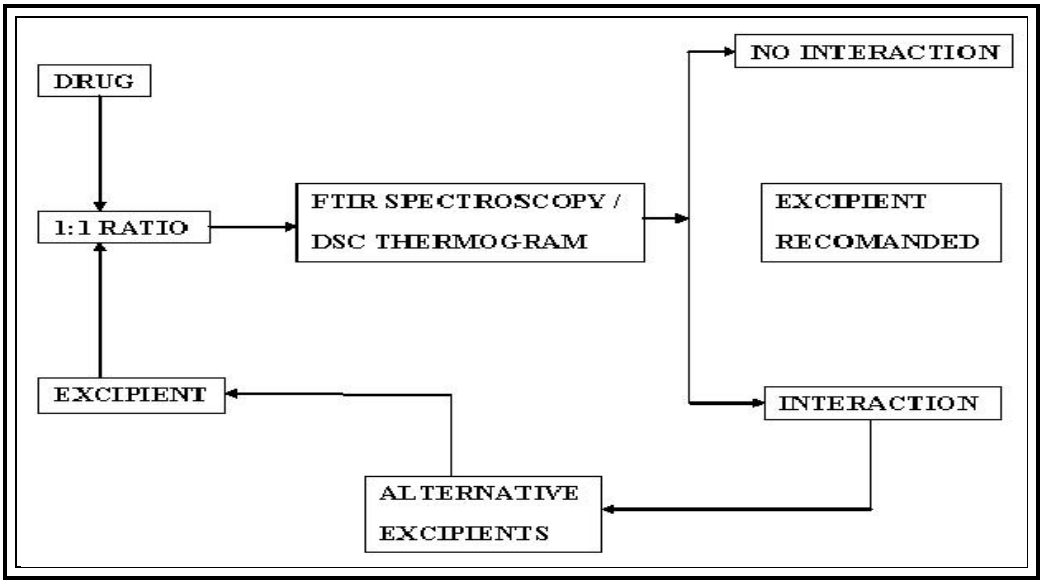


Figure 7.1: Schematic representation of compatibility studies

7.1.4. b) Fourier transform Infra-Red (FTIR) spectroscopy *(IP, 2007)*

FTIR study was carried out to check compatibility of drug with polymers. Fourier transform Infrared Spectrophotometer was determined by using KBr dispersion method. The base line correction was done using dried potassium bromide. Then the spectrum of dried mixture of Quetiapine and potassium bromide was run followed by Quetiapine with various polymers by using FTIR spectrophotometer. The absorption maximums in spectrum obtained with the substance being examined correspond in position and relative intensity to those in the reference spectrum was represented in Table 8.6 and shown in Figure 8.4, 8.5, 8.6 and 8.7.

7.1.4. c) Differential scanning calorimetry (DSC) **(***AultonM.E., et al.,2002)*

Any possible drug polymer interaction can be studied by thermal analysis. The DSC study was performed on pure Quetiapine, Quetiapine + HPMC K15M, Quetiapine + carbopol-974P and Quetiapine + sodium alginate. The 2 mg of sample were heated in a hermetically sealed aluminum pans in the temperature range of 25-300ºC at heating rate of 10ºC /min under nitrogen flow of 30ml/min. The results of DSC analysis were represented in Table 8.7and showed in Figure 8.8, 8.9, 8.10 and 8.11.

7.2. METHOD OF PREPARATION OF QUETIAPINE MICROSPHERES

Table 7.1: Formulation of quetiapine fumarate microspheres

S.No.	Batch.No.	Drug (g)	Sodium alginate (%)	HPMC K15M (%)	Carbopol 974 p (%)
1	QF1	1	1.5	-	-
2	QF2	1	2.5	-	-
3	QF3	1	3.5	-	-
4	QF4	1	1.5	2	-
5	QF5	1	2.5	2	-
6	QF6	1	3.5	2	-
7	QF7	1	1.5	-	1
8	QF8	1	2.5	-	1
9	QF9	1	3.5	-	1

7.2.1. Orifice ionic gelation method (syringes method) *(Swamy P.V., et al., 2007)*

In this technique cross linking of sodium alginate is done with calcium chloride solution to release the drug in a controlled manner. Chemically alginates are anionic block co-polymer consisting monomers of d – mannoic acid joined together by 1-4 glycosidic linkages. Bivalent alkaline earth metals like calcium undergoes ionic interaction with COOH moiety of sodium alginate and results are in cross linking of sodium alginate. Microspheres were prepared by using the technique in which sodium

alginate in different ratios as mentioned then added mucoadhesive polymers was slowly added to the above solution with continuous stirring to form homogenous solution.

After the aqueous sodium alginate solution by sonicating the mixture for 20 minutes the drug substance Quetiapine fumarate was then added to the above solution to form a clear solution (polymer – alginate mixture). The drug polymer mixture is dispersion was poured in 15% calcium chloride solution using 22# needle by stirring at 50rpm the microspheres thus formed are allowed 30 min for curing in calcium chloride solution then were decanted and washed with distilled water and air dried over night at room temperature.

The flow chart of preparation of Quetiapine microspheres

Sodium alginate + Quetiapine+ Polymer
↓ Added
Calcium chloride
↓ To form
Microspheres

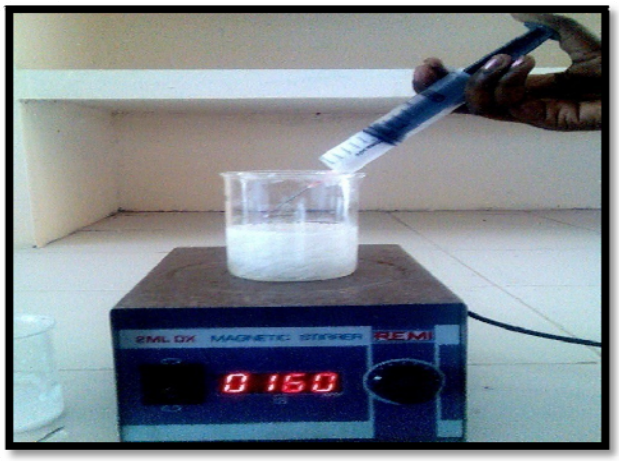


Figure.7.2: Preparation of microspheres using 21# syringe needle in magnetic stirrer

7.3. EVALUATION AND CHARACTERIZATION OF MICROSPHERES

(BhabaniNayak S., et al., 2009; Stephen Rathinaraj., et al., 2010)

Appropriate assessment of a dispersed system requires characterization of both chemical and physical stabilities. Physical properties are very important with respect to the performance of dispersed systems.

7.3.1. Particle Size Determination *(Subramanayam C. V .S;SwamyP.V,.et al., 2007)*

Particle size distribution for the microspheres were measured by sieving method analysis, using set of standard sieves was weighed. Particles having size range between 50 and 1500 μm are estimated by sieving method. This method directly gives weight distribution. The sieving method is a useful application in dosage form development of tablets and spheres

7.3.2. Percentage Yield *(BhabaniNayak S., et al., 2009)*

The total amount of microspheres obtained were weighed and evaluated for percentage yield.

$$\text{Percentage yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

7.3.3. Drug content estimation and Encapsulation efficiency

(Swamy P.V, et al., 2007; Dandagi P M., et al.,2004)

Quetiapine microspheres (100mg) from each batch were initially stirred in 3 ml sodium citrate solution (1%w/v) until complete dissolution. A quantity of 7 ml of methanol was added to above solution to solubilise calcium alginate and further solubilise

the Quetiapine. The filtrate was assayed for drug content by measuring the absorbance at 293.5 nm after suitable dilution by UV-Visible spectrophotometer and

Encapsulation efficiency was calculated using the formula,

$$\text{Encapsulation efficiency} = \frac{\text{Estimated \% drug content in microspheres}}{\text{Theoretical \% drug content in microspheres}} \times 100$$

7.3.4. Percentage moisture content: *(BhabaniNayak S., et al., 2009)*

The Quetiapine loaded microspheres was evaluated to determine the percentage moisture content which sharing an idea about its hydrophilic nature. The microspheres weighed (w_1) initially kept in desicator containing Calcium chloride at 37º C for 24 hours. The final weight (w_2) was noted when no further change in weight of sample was observed.

$$\text{Moisture Percentage} = \frac{w_1 - w_2}{w_2} \times 100$$

7.3.5. Scanning electron microscopy (SEM): *(SwamyP.V,.et al.,2007)*

The microspheres were observed under a Scanning Electron Microscopy. They were mounted directly onto SEM sample stub using double-sided sticking tape and coated with gold film with ion spillter with gold target with resolution 3 nm (30 KV HV Mode),10 nm (30 KV HV Mode), 40 nm (30 LV Mode) and a vacuum system is fitted to it.

7.3.6. *In -vitro* wash off test for mucoadhesion:

(Stephen Rathinaraj., et al., 2010; Mohammed G Ahmed., et al., 2010)

The mucoadhesive property of the Quetiapine fumarate microspheres was evaluated by an *in -vitro* adhesion testing method known as the wash – off method. Freshly excised pieces of intestinal mucosa (4×5 cm) from sheep were mounted onto glass slides (3×1inch) with poly cyanoacrylate glue. Two glass slides were connected with a suitable each wet rinsed tissue specimen, and immediately thereafter the support were hung onto the arm of a USP tablet disintegrating test machine. When the disintegrating test machine was operated, the tissue specimen was given a slow, regular up and down movement in the test fluid (400ml) at 37ºC contained in a 1000 ml vessel of the machine. At the end of 1 hr and at hourly interval up to 8 hr, the machine was stopped and the number of microsphere still adhering to the tissue was counted. The test was performed in simulated intestinal fluid (pH6.8 phosphate buffer).

7.3.7 .*In- vitro* drug release studies

(USP, 2009; SwamyP.V.,et al., 2007;Chowdary K. P. R., et al., 2003)

In-vitro drug release study was carried out in USP dissolution test apparatus. A quantity of microspheres equivalent to 100 mg of Quetiapine fumarate microspheres was kept in basket type apparatus and immersed in 900ml of phosphate buffer (pH 6.8) in 1000 ml dissolution flask and temperature was maintained at 37 ± 0.5ºC throughout the study. At predetermined time intervals 2 ml of samples was withdrawn by means of a syringe fitted with prefilter and same was replaced into the dissolution flask containing pH 6.8. The absorbance of sample was measured at 293.5 nm after required dilution with the fresh medium (pH6.8).All the studies were conducted in triplicate.

7.3.8. Kinetics of *In-vitro* drug release

(Swamy P.V., et al., 2007; BhabaniNayakS.,et al.,2009)

In-vitro drug released data was subjected to *in- vitro* kinetic models such as zero order, first order, Higuchi and Korsemeyer- Peppas.

- **Zero order:** $C = K_0 t$

Where K_0 - is the zero-order rate constant expressed in units of concentration/time

t -is the time in hrs.

- **First order:** $Log\ C = LogC_0 - Kt / 2.303$

Where C_0 - is the initial concentration of drug,

K - is the first order constant

t - is the time in hrs.

- **Higuchi:** $Qt = Kt^{1/2}$

Where Q_t - is the amount of the release drug in time t,

K- is the kinetic constant and t- is time in hrs

- **KorsmeyerPeppas:** $Mt/ M\infty = Kt\ n$

Where M_t - represents amount of the released drug at time t,

M_∞- is the overall amount of the drug (whole dose) released after 12 hrs

K- is the diffusional characteristic of drug/ polymer system constant

n- is a diffusional exponent that characterizes the mechanism of release of drug.

Table 7.2: Diffusion exponent and solute release mechanism

Diffusion exponent (n)	Overall solute diffusion mechanism
< 0.5	Quasi-Fickian diffusion
0.5	Fickian diffusion
0.5 < n < 1.0	Anomalous (non-Fickian) diffusion
1.0	Case-II transport
> 1.0	Super case-II transport

7.4. STABILITY STUDY

(Manavalan R. and Ramasamy S., 2004, Europeon Medicine agency, CPSEA, ICH Q1 A (R2) guidelines)

In any rational drug design or evaluation of dosage forms, the stability of the active component was a major criterion in determining their acceptance or rejection.

Objective of the study

The purpose of stability testing was to provide the evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives. The International Conference on Harmonization (ICH) Guidelines titled "Stability testing of New Drug Substances and Products describes the stability test requirements for drug registration application in the European Union, Japan and the States of America.

ICH specifies the length of study and storage conditions

- **Long-Term Testing**: Room temperature ;25 °C ±2 °C at 60% RH ±5% for 12 months
- **Accelerated Testing:** Accelerated temperature **;**40 °C ±2 °C at 75% RH ±5% for 6 Months

In present study the optimized formulation F9 was exposured up to 3 months stability studies at accelerated condition (40 °C ±2 °C at 75% RH ±5%RH) to find out the effect of aging on drug content and *In-vitro* drug release.

Procedure

The formulation (F9) was stored at accelerated condition in aluminum foils for 3 months. The samples were withdrawn after end of 1st month, 2nd month and 3rd month. The samples were analyzed for its drug content and i*n vitro* drug release.

RESULTS AND DISCUSSION

8. RESULTS AND DISCUSSION

8.1. PREFORMULATION PARAMETERS

8.1.1. Identification of drug

8.1.1. a) Identification by FTIR spectroscopy

The FTIR spectrum of Quetiapine was shown in Figure 8.1 and the interpretations of IR frequencies were represented in Table 8.1.

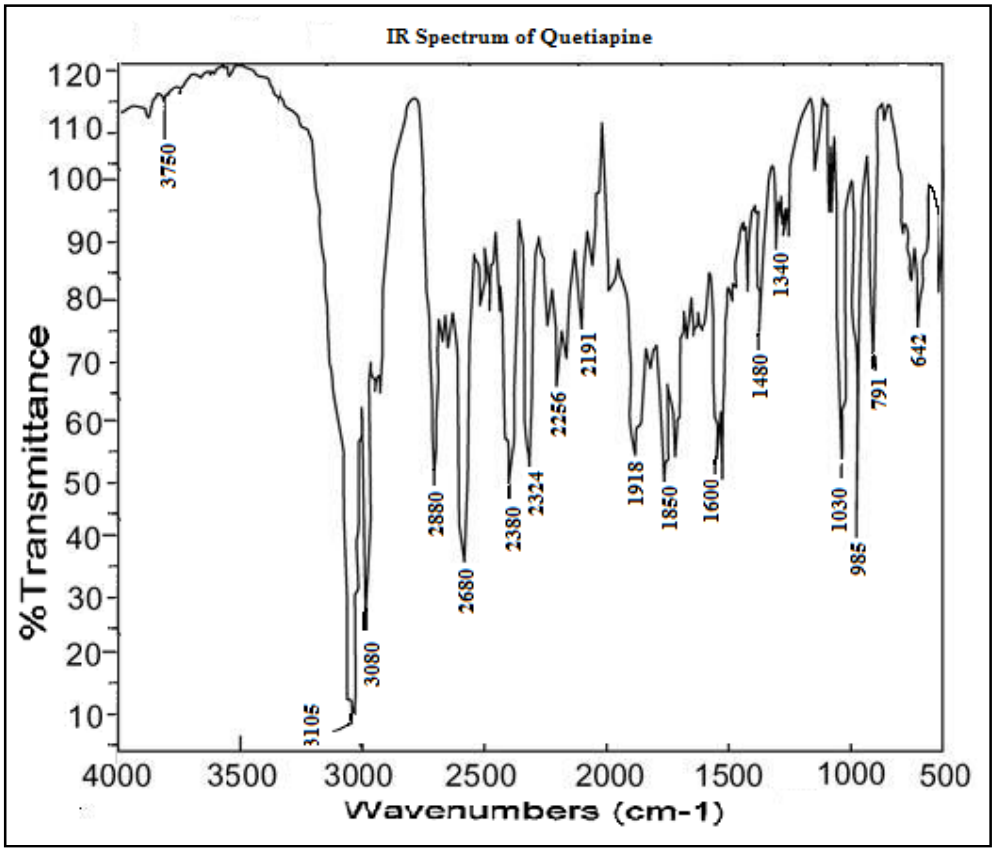


Figure 8.1: FTIR spectrum of quetiapine

- **Interpretation of FTIR Spectrum**

Major functional groups present in Quetiapine show characteristic peaks in FTIR spectrum. The major peaks are identical to functional group of Quetiapine Hence, the sample was confirmed as Quetiapine.

Table 8.1: Characteristic frequencies in FTIR spectrum of quetiapine

Inference	**Wave no.(cm^{-1})**
O-H stretching	3750
Aromatic C-H stretching	3080
C-H stretching	2880
Aromatic C=C stretching	2380
C-N Stretching	1600
C-H bending	1340
C-O-C stretching	1030
Benzene ring	791

8.1.1. b) Melting point

Melting point values of Quetiapine sample was found to be in range of 172° C to 174° C .The reported melting point for Quetiapine was 173^0 C. Hence, experimental values were same as official values.

8.1.2. Physicochemical parameters of drug

8.1.2. a)Organoleptic properties

Odour: Odourless

Colour: White colour

Nature: crystalline powder

8.1.2. b) Solubility study

Table 8.2: Solubility of quetiapine in various solvents

Name of solvent	Standard Parts of solvent required for part of solute	Solubility
Distilled water	From 30 to 100	Slightly Soluble
0.1N HCl	From 30 to 100	Slightly Soluble
Ethanol (95%)	From 1 to 30	Highly soluble
Methanol	From 1 to 30	Highly Soluble
Isopropyl alcohol	More than 10000	Partially insoluble
Glacial acetic acid	More than 10000	Partially insoluble
Acetone	More than 10000	Partially insoluble

8.1.3. Analytical methods

8.1.3. a) Determination of λ max

The absorption maximum for quetiapine was found at 293.5nm

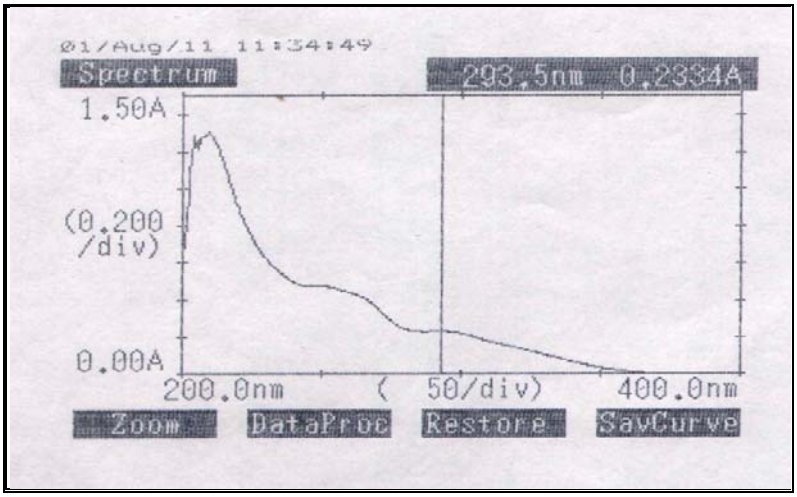


Figure 8.2: λ max observed for quetiapine fumarate in pH 6.8 (phosphate buffer).

8.1.3. b) Preparation of standard graph of Quetiapine fumarate

UV absorption spectrum of Quetiapine fumarate in phosphate buffer (pH 6.8) showed λ max at 293.5 nm. Absorbance obtained for various concentrations of Quetiapine fumarate in pH 6.8 were represented in Table 8.3. The graph of absorbance vs. concentration for Quetiapine fumarate was found to be linear in the concentration range of 5–30 µg/ml. The drug obeys Beer- Lambert's law in the range of 5–30 µg /ml.

Table 8.3: Data of concentration and absorbance for quetiapine fumarate in pH 6.8 buffer

S.No.	Concentration (µg/ml)	Absorbance
1	0	0.000
2	5	0.097
3	10	0.189
4	15	0.291
5	20	0.387
6	25	0.483
7	30	0.587

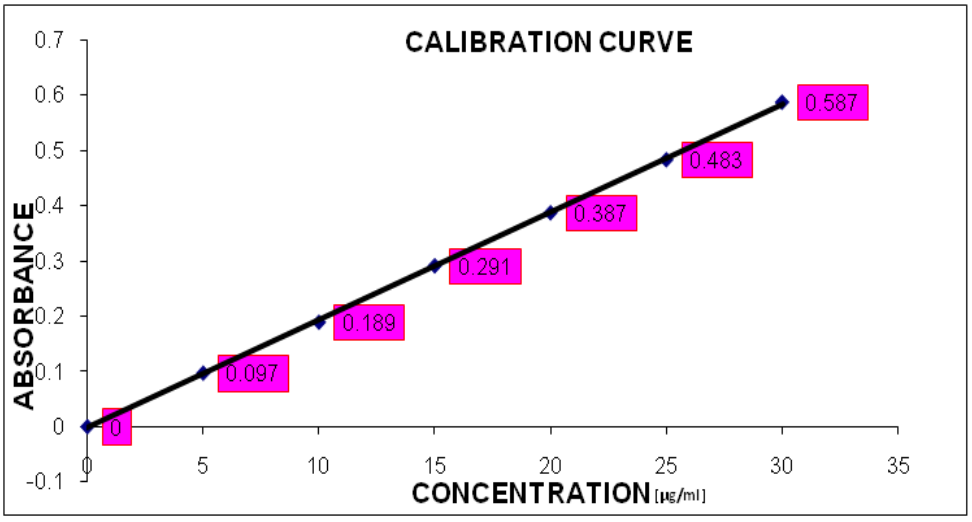


Figure 8.3: Standard curve for quetiapine fumarate in pH 6.8 (phosphate buffer)

Table 8.4: Data for calibration curve parameters

S. No.	Parameters	Values
1	Correlation coefficient (r)	0.9999
2	Slope	0.019507
3	Intercept	-0.00204

8.1.3. c) Percentage purity of drug

The percentage purity of drug was calculated by using calibration graph method (least square method).

Table 8.5: Data of percentage purity of drug

S. No.	Percentage purity (%)	Avg. percentage purity (%)
1	99.71	100.4
2	100.51	
3	101.10	

The reported percentage purity for Quetiapine fumarate in USP is 98 to 102%.

8.1.4. Determination of compatibility for drug with polymer

8.1.4. a) FTIR spectroscopy

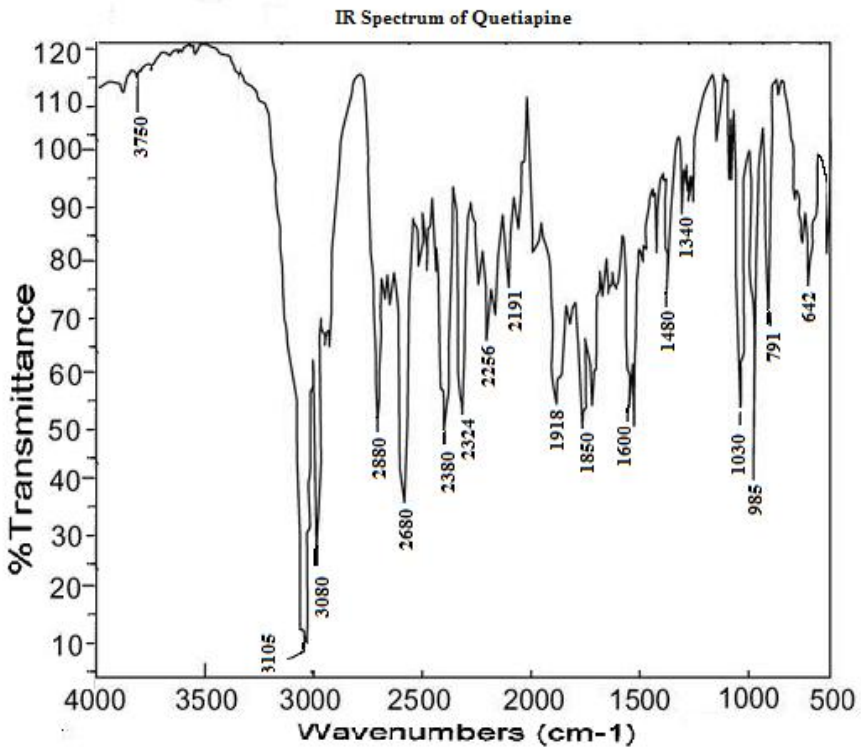


Figure 8.4: FTIR spectrum of quetiapine

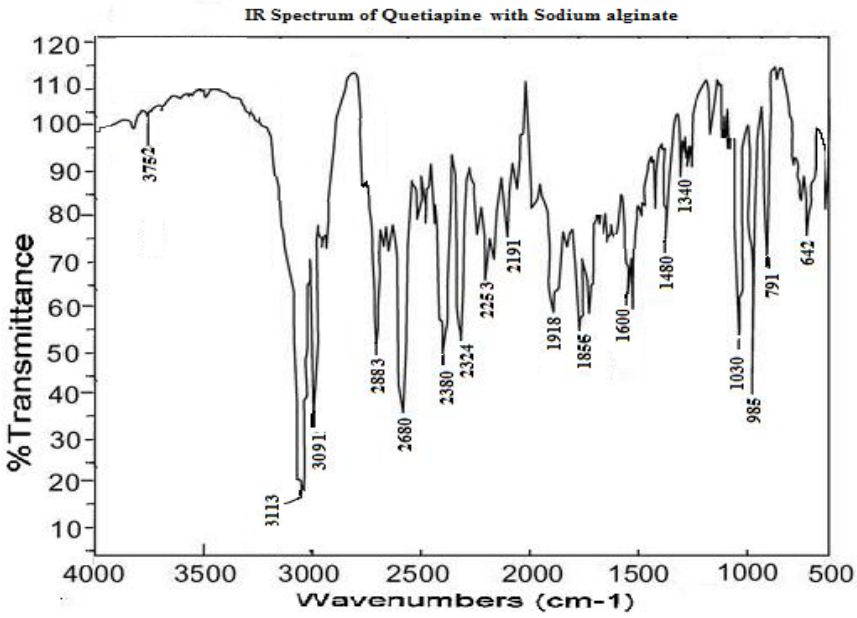


Figure 8.5: FTIR spectrum of Quetiapine with Sodium alginate

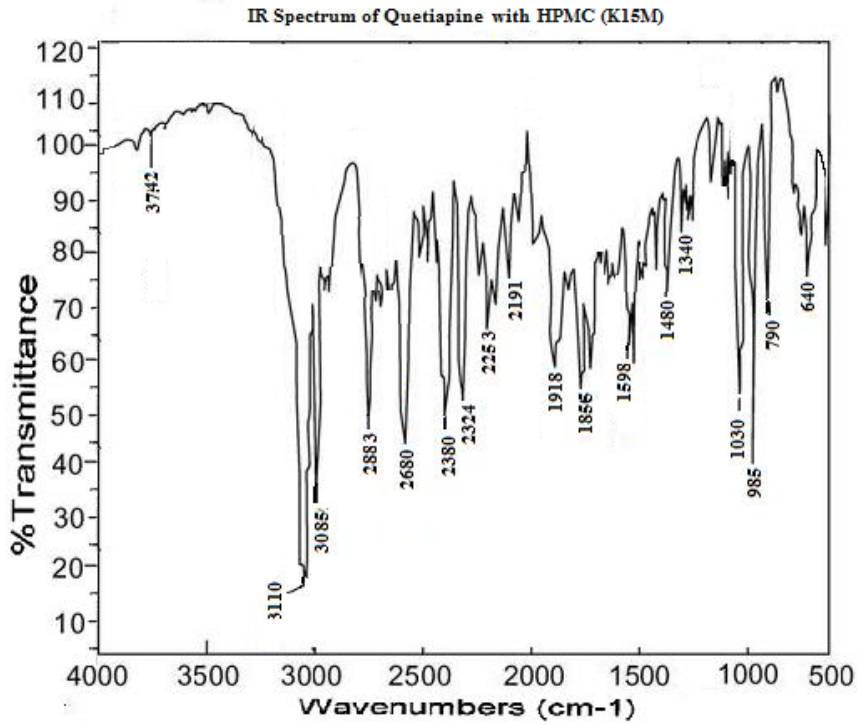


Figure 8.6: FTIR spectrum of quetiapine with HPMC K15M

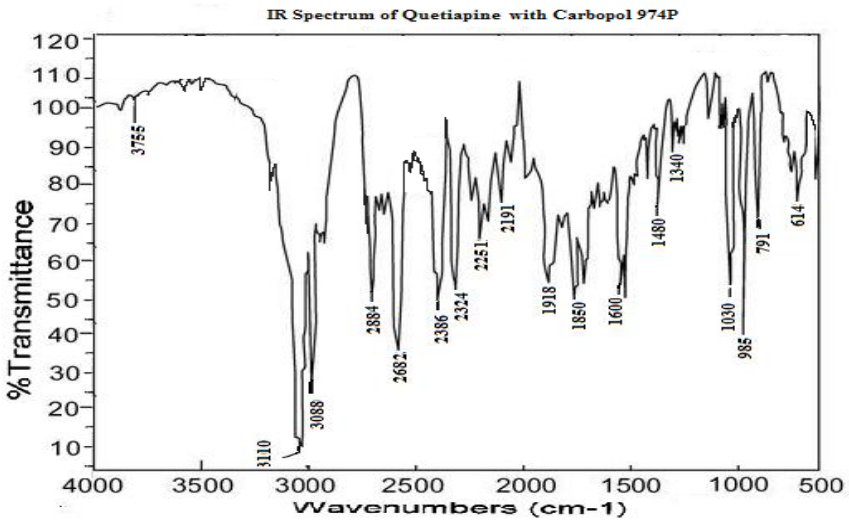


Figure 8.7: FTIR spectrum of quetiapine with carbopol 974p

Table 8.6: The major peak observed in FTIR spectrum of quetiapine and quetiapine with different polymers used in formulations.

Wave No. (cm^{-1})	**Functional group**	**Peak observed (Yes/No)**			
		Quetiapine	**Quetiapine+ Sodiumalginate**	**Quetiapine+ HPMC K15M**	**Quetiapine+ Carbopol974p**
3750	O-H stretching	**Yes**	**Yes**	**Yes**	**Yes**
3080	Aromatic C-H stretching	**Yes**	**Yes**	**Yes**	**Yes**
2880	C-H stretching	**Yes**	**Yes**	**Yes**	**Yes**
2380	Aromatic C=C stretching	**Yes**	**Yes**	**Yes**	**Yes**
1600	C-N Stretching	**Yes**	**Yes**	**Yes**	**Yes**
1340	C-H bending	**Yes**	**Yes**	**Yes**	**Yes**
1030	C-O-C stretching	**Yes**	**Yes**	**Yes**	**Yes**
791	Benzene ring	**Yes**	**Yes**	**Yes**	**Yes**

The major peaks of Quetiapine fumarate spectrum were compared to Quetiapine fumarate with polymers spectrum. There was no interaction between Quetiapine fumarate and polymers. The data was represented in Table 8.6 and shown in Figure 8.4, 8.5, 8.6 and 8.7.

8.1.4. b) DSC thermal analysis: The interactions between Quetiapine and polymers were determined by DSC studies and results were represented in Table 8.7 and shown Figure 8.8, 8.9, 8.10 and 8.11.

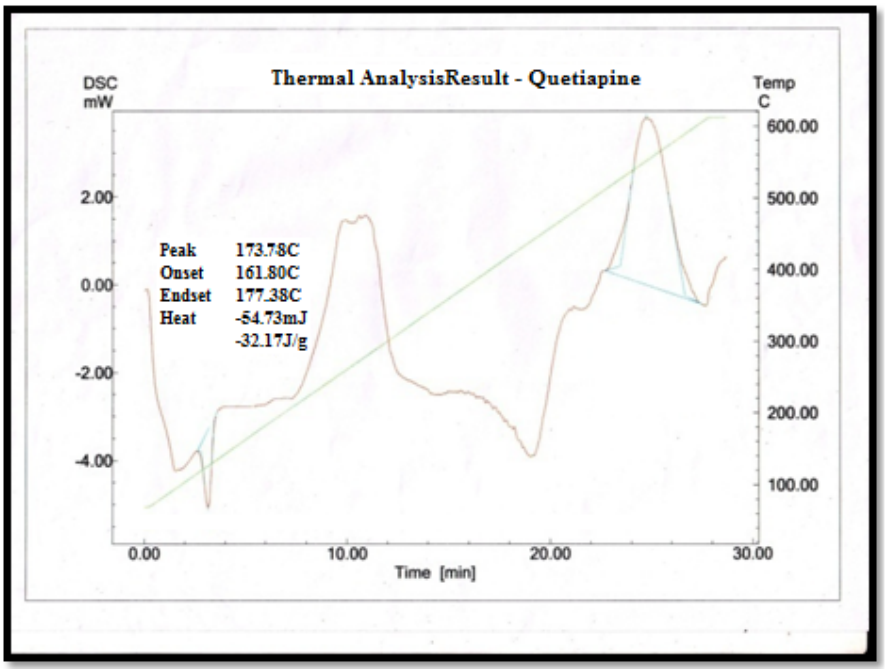


Figure 8.8: DSC thermogram for quetiapine fumarate

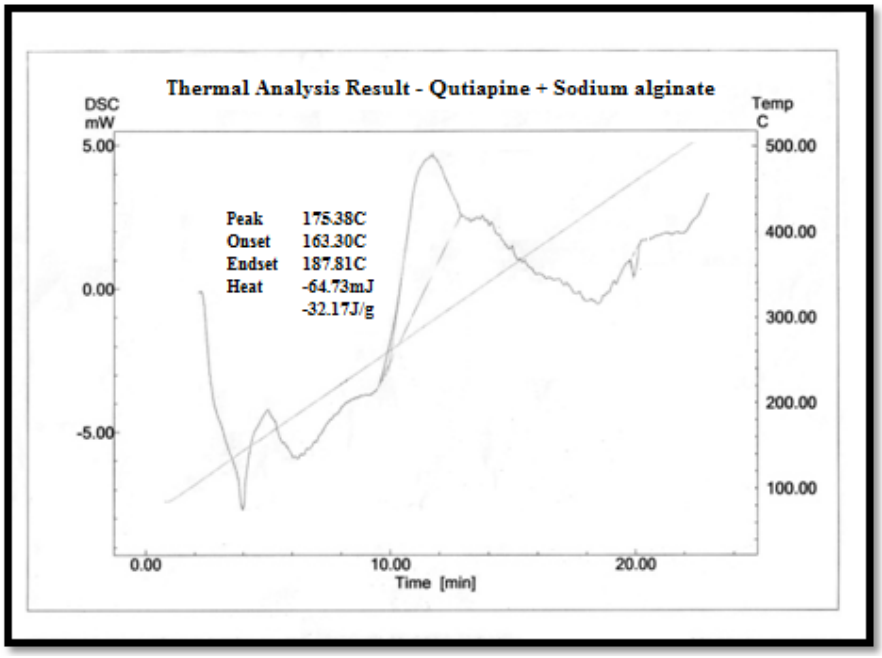


Figure 8.9: DSC thermogram for quetiapine fumarate with Sodium alginate

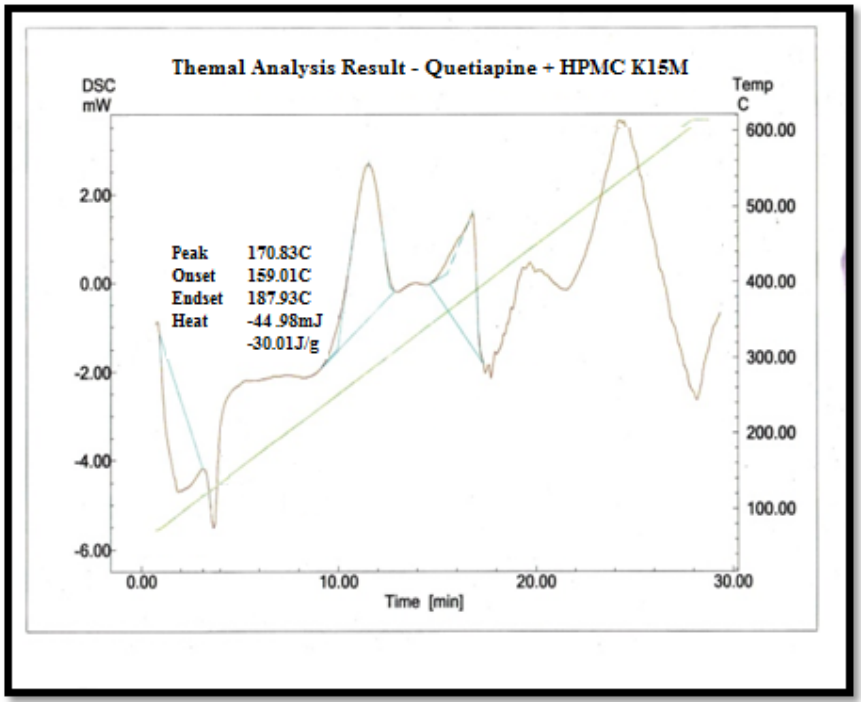


Figure 8.10: DSC thermogram for quetiapine fumarate with HPMC K15M

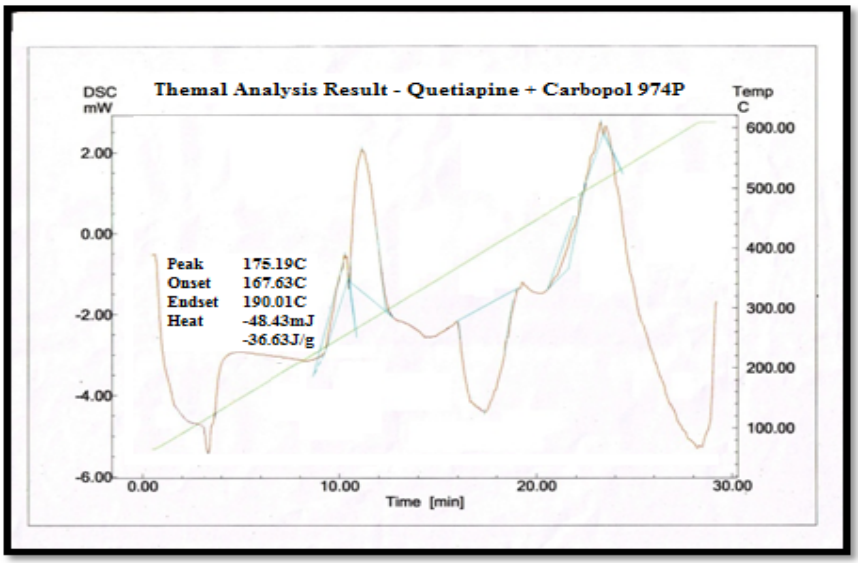


Figure.8.11: DSC thermogram for quetiapine fumarate with carbopol 974P

Table 8.7: Various DSC thermogram parameter

S. No.	DSC Graphs	Peak (ºC)	Onset temperature (ºC)	Endset temperature (ºC)
1	Quetiapine fumarate	173.70	161.80	177.38
2	Quetiapine + sodium alginate	175.38	163.30	181.81
3	Quetiapine + HPMC k15M	170.83	159.01	187.93
4	Quetiapine + carbopol 974p	175.19	167.63	190.01

From the DSC thermograms, there was no major difference in onset temperature, endset temperature and peak temperature compared to pure Quetiapine thermogram. Therefore no interaction found between the Quetiapine with polymers.

PREPARED MICROSPHERES BY ORIFICE-IONIC GELATION METHOD:

The microspheres prepared by the orifice-ionic gelation method were shown in Figure 8.12 and microspheres after drying process were shown in Figure 8.13.

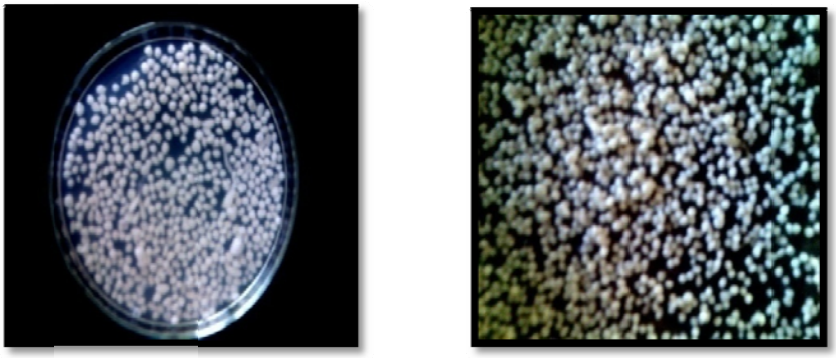


Figure 8.12: Prepared microspheres by orifice –ionic gelation method

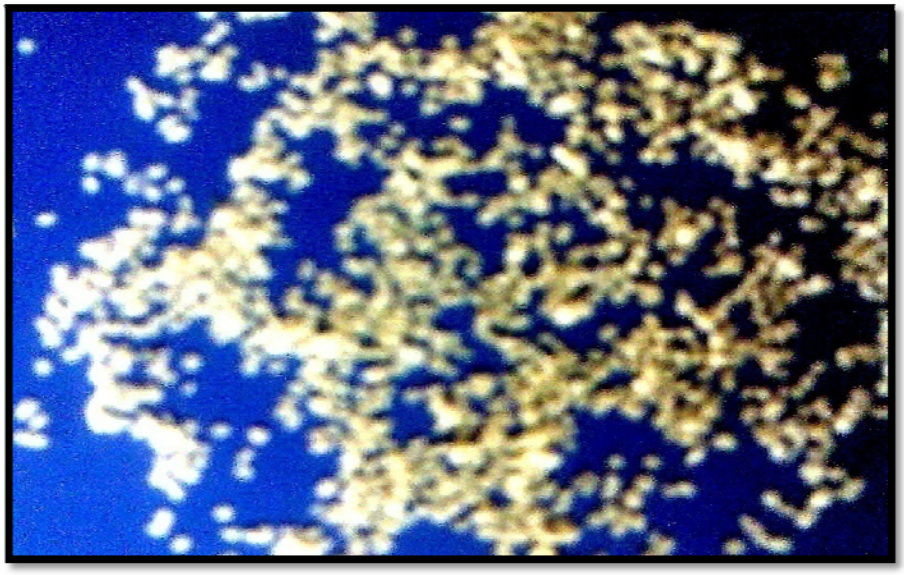


Figure.8.13: Prepared microspheres after the process of drying 12 hrs

8.2. EVALUATION OF QUETIAPINE LOADED MUCOADHESIVE MICROSPHERES

- Percentage yield
- Size analysis
- Drug content estimation and Encapsulation efficiency
- Percentage moisture content
- Scanning electron microscopy
- *In vitro* wash –off test for mucoadhesion
- *In vitro* drug release studies

8.2.1. Percentage yield

The total amount of microspheres obtained were weighed and evaluated for percentage yield and represented in Table 8.8 .From this, formulation F8 showed maximum percentage yield among the formulations prepared.

Table 8.8: Percentage yield of all microspheres formulations

S. No	Formulation Code	Percentage yield (%)
1.	F1	75.19
2	F2	77.40
3	F3	73.20
4	F4	82.20
5	F5	82.00
6	F6	71.60
7	F7	65.60
8	F8	87.95
9	F9	88.65

8.2.2. Particle size determinations

Average particle size of microspheres was determined for all the formulations by sieving method analysis by using standard sieves. All the values were represented in Table 8.9. From the values, the formulation F9 had given the less average particle size compared to all other formulation

Table 8.9: Average particle size of microspheres

S. No	Formulations	Average particle size (µm)
1	F1	602.28
2	F2	650.18
3	F3	770.74
4	F4	708.268
5	F5	740.578
6	F6	784.506
7	F7	650.85
8	F8	680.31
9	F9	754.34

8.2.3. Drug content estimation and encapsulation efficiency

Quetiapine microspheres (100 mg) from each batch were initially stirred in 3 ml sodium citrate solution (1%w/v) until it completely dissolves .A quantity of methanol 7ml was added to above solution to gel solubilise calcium alginate and further solubilise Quetiapine. The filtrate was assayed for drug content by measuring the absorbance at 293.5 nm after suitable dilution. Encapsulation efficiency was

calculated using the formula. The drug content of microspheres were calculated for all the formulations (F1 to F9) and represented in Table 8.10 also shown in Figure 8.14.The formulation F9 was showed maximum drug content among the formulations were prepared

$$\text{Encapsulation efficiency} = \frac{\text{Estimated \% drug content in microspheres}}{\text{Theoretical \% drug content in microspheres}} \times 100$$

Table 8.10: Drug content of all microspheres formulations

S. No	Formulations	Mean drug content (%) ± S.D*	Entrapment efficiency (%)
1	F1	31.210 ± 0.039	63.42
2	F2	40.120± 0.058	79.25
3	F3	42.476± 0.045	83.95
4	F4	40.418± 0.014	81.83
5	F5	41.990± 0.018	82.90
6	F6	42.770± 0.051	85.54
7	F7	35.610±0.063	70.22
8	F8	34.730±0.004	68.46
9	F9	43.96± 0.085	87.70

*All values are expressed as mean ± S.D. n=3

The mean drug contents were obtained from formulations F1-31.2%, F2 - 40.12%, F3 - 42.48%, F4 - 40.14%, F5 - 41.99%, F6 - 42.77%, F7 - 35.61%, F8 - 34.73%, F9 - 43.96% and the entrapment efficiency were F1 - 63.42%, F2 - 79.25%, F3 - 83.95%, F4 - 81.83%, F5 - 82.90%, F6 - 85.54%, F7 - 70.22%, F8 - 68.46.%,F9 - 87.70%. Among all formulations F9 showed best results compared to all other formulations.

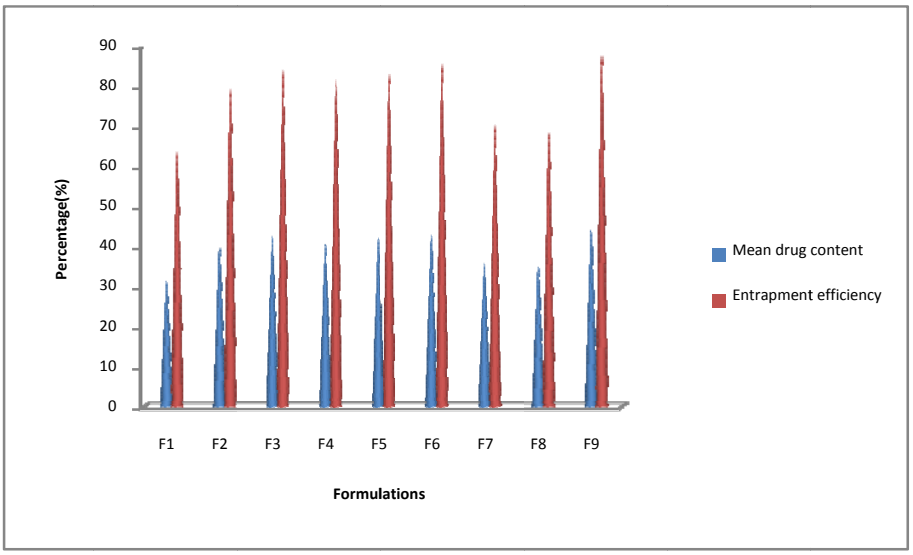


Figure 8.14: Comparison of drug content and entrapment efficiency

8.2.4. Percentage moisture content

The percentage moisture content was calculated for all the formulations (F1 to F9) by using dessicator containing Calcium chloride at 37°C for 24 hrs. The final weight was determined and compared to initial weight .The values were represented in Table 8.11.

$$\text{Percentage Moisture content} = \frac{w_1 - w_2}{w_2} \times 100$$

Table 8.11: Percentage moisture content of microspheres

S. No	Formulations	Percentage moisture content (% ± S.D)
1	F1	8.273±0.155
2	F2	6.837± 0.078
3	F3	4.876± 0.090
4	F4	3.258± 0.141
5	F5	2.529± 0.050
6	F6	1.838± 0.063
7	F7	2.516±0.040
8	F8	1.244±0.130
9	F9	1.116±0.130

*All values are expressed as mean ± S.D. n=3

By comparing all the values of all formulations, formulation F9 was found to be the best one. The formulation F9 showed less moisture content. The order was F9<F8<F6<F7<F5<F4<F3<F2<F1.

8.2.5. Scanning electron microscopy (SEM)

The microspheres were observed under a scanning electron microscopy. The resolution of SEM instrument was 3 nm (30 KV HV Mode), 10 nm (30 KV HV Mode), 40 nm (30 LV Mode) and a vacuum system is fitted to it. The shape of the Quetiapine microspheres was evidenced from the Scanning Electron microscopy was

found to be spherical and uniformly distributed and was shown in Figure 8.15 and 8.16.

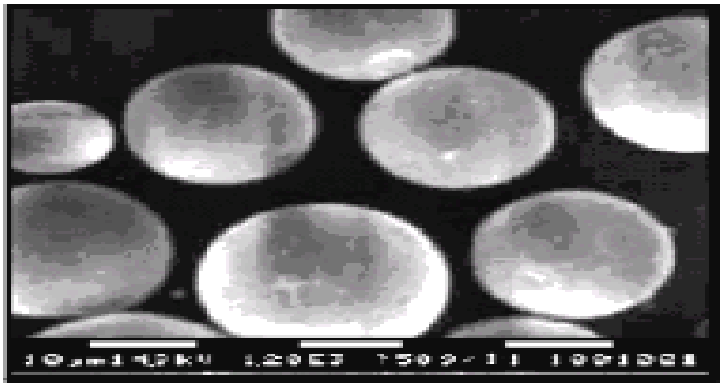


Figure 8.15: Scanning electron microscopy of drug loaded sodium alginate carbopol 974P

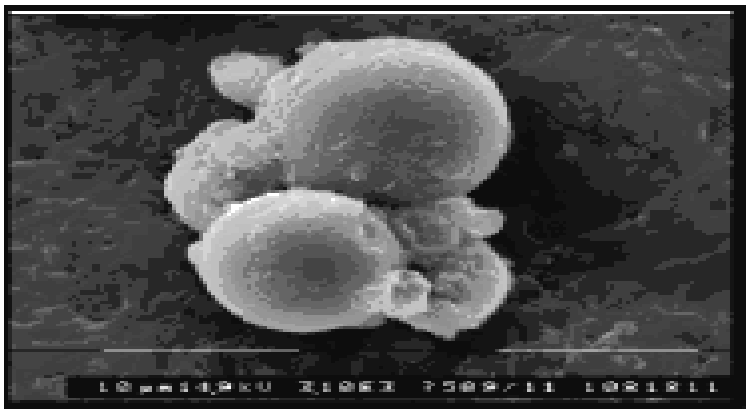


Figure 8.16: Scanning electron microscopy of formulation F9.

8.2.6. *In vitro* wash off test for mucoadhesion

The wash off test for mucoadhesion for all formulations (F1 to F9) were represented in Table 8.12 and graphically shown in Figure 8.17.

The mucoadhesive wash off test was showed in the order of F1<F6<F4<F2<F3<F5<F7<F8<F9. Low values of standard deviation indicate good mucoadhesion in each batch of microspheres.

Table 8.12: Data of *in- vitro* wash off test to assess mucoadhesive properties of microspheres

% of Microspheres adhering to the tissue at various time interval* in 8 hours						
Formulations	**pH**	**1(hr)**	**2(hr)**	**4(hr)**	**6(hr)**	**8(hr)**
F1	6.8	97.8±0.1	89.9±0.6	86.2±0.9	59.4±0.6	41.7±1.6
F2	6.8	97.3 ±0.9	90.3±0.9	87.6±2.0	60.5±1.2	44.5±2.0
F3	6.8	96±1.07	91±0	87±2.0	72.3±1.2	52.3±1.8
F4	6.8	98±2.0	95.6±1.2	85.3±3.3	79±2.0	43.6±2.2
F5	6.8	98±2.1	95.2±1.2	90.5±2.0	78.7±1.9	55.2±1.5
F6	6.8	98.6±2.0	96.6±1.2	92.6±1.2	72.9±1.2	42.1±1.5
F7	6.8	98.4±2.0	97±1.2	90.3±2.0	62.9±1.2	59.5±3.5
F8	6.8	99± 1.3	97±0	91.6±1.2	79.9±1.9	61.3±1.2
F9	6.8	100±0	97.3±0.9	92.6±2.0	84.2±3.1	64.9±1.2

*All values are expressed as mean ± S.D. n=3

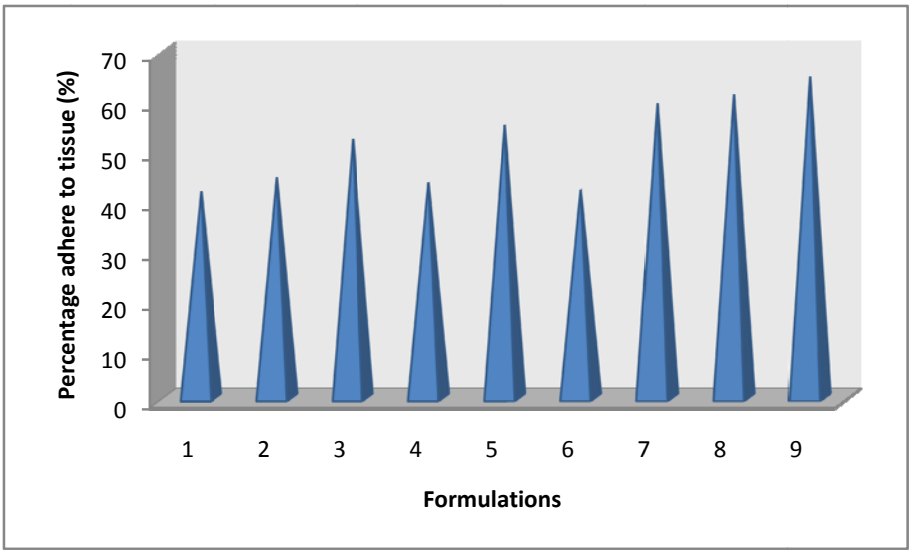


Figure 8.17: *In vitro* mucoadhesive wash off test graphical representation

Microspheres with a coat consisting of alginate and a mucoadhesive polymer exhibited good mucoadhesive properties in the *in- vitro* wash off test. The wash off test was faster at a pH 6.8 (intestinal pH). It was observed that the pH of the medium was critical for the degree of hydration, solubility and mucoadhesion of the polymers.

The results of the wash off test indicated that the formulation F9 had very good mucoadhesive properties with more than 64.9% retention for 8 hrs in phosphate buffer (pH 6.8).

8.2.7. *In vitro* drug release studies

Table.8.13: Results of in vitro release studies of quetiapine loaded mucoadhesive microspheres* at 12 hours

S. No	Time in hours	Formulation code								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	1	10.92 ±0.11	10.06 ±1.54	9.07± 1.04	10.24± 1.54	9.65± 1.56	10.48± 0.45	10.48 ±2.78	9.81± 0.45	8.36± 1.54
2	2	22.35 ±1.23	21.78 ±1.89	19.75 ±2.66	21.81± 0.61	20.18 ±1.05	18.96± 0.15	18.45 ±1.96	17.73 ±0.55	15.88 ±1.45
3	3	28.39 ±2.54	28.49 ±2.54	26.29 ±0.20	29.93± 0.02	28.5± 3.51	27.96± 1.63	27.96 ±0.12	24.11 ±0.56	22.18 ±1.52
4	4	40.59 ±1.56	36.28 ±1.65	35.97 ±1.53	41.92± 0.91	40.22 ±1.55	31.18± 3.55	31.18 ±0.56	30.02 ±0.22	29.39 ±0.01
5	5	43.29 ±2.57	42.36 ±0.22	40.49 ±2.01	48.76± 0.78	45.49 ±0.45	39.26± 2.23	39.26 ±1.56	37.9± 1.51	35.48 ±0.12
6	6	55.82 ±0.23	55.48 ±2.55	51.29 ±2.50	55.25± 0.51	52.06 ±0.61	48.38± 1.25	48.38 ±3.45	47.66 ±1.02	40.19 ±0.65
7	7	63.92 ±1.54	57.39 ±0.23	58.39 ±1.21	59.38± 0.05	57.19 ±0.49	51.9±0 .61	51.9± 1.56	50.04 ±2.55	48.99 ±0.54
8	8	69.94 ±2.45	68.39 ±2.55	62.01 ±0.54	70.69± 0.07	68.24 ±0.61	62.01± 0.74	62.01 ±1.26	58.46 ±2.16	55.38 ±1.55
9	9	74.26 ±2.77	71.01 ±2.54	69.45 ±0.26	75.2±0 .48	74.39 ±1.54	65.33± 0.07	65.33 ±0.16	62.09 ±2.55	61.47 ±0.65
10	10	87.28 ±2.54	90.37 ±2.54	81.92 ±0.50	82.19± 0.52	80.27 ±0.91	81.53± 0.21	81.53 ±1.51	82.19 ±2.16	71.24 ±0.55
11	11	90.22 ±3.45	95.2± 2.56	93.28 ±0.78	88.36± 0.46	86.33 ±0.61	84.74± 0.51	84.74 ±2.51	86.28 ±2.55	76.92 ±1.56
12	12	98.36 ±0.54	97.62 ±0.59	97.04 ±0.49	96.35± 0.65	95.14 ±0.61	92.37± 0.45	90.37 ±0.54	85.37 ±2.15	79.3± 1.56

*All values are expressed as mean ± S.D. n=3

➢ **Dissolution profile of formulation F1**

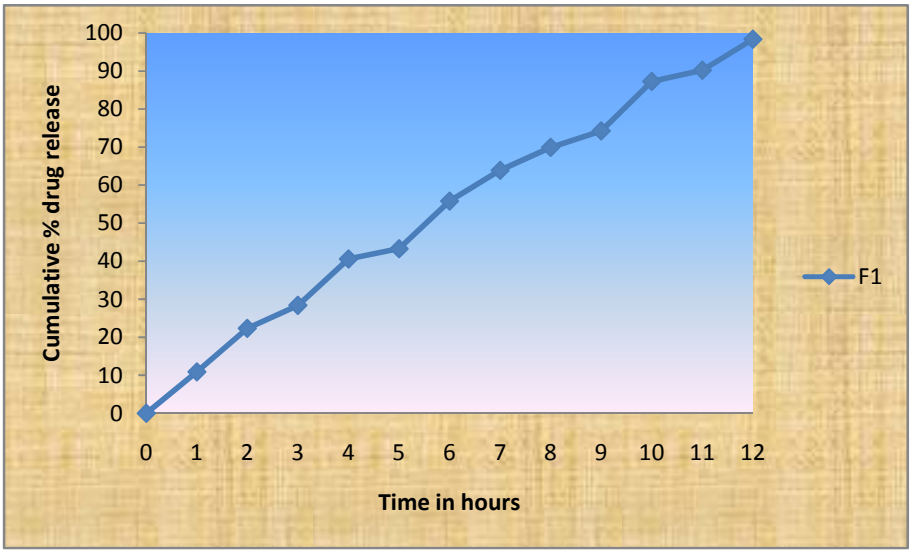


Figure 8.18 : *In vitro* released graph of formulation F1

➢ **Dissolution profile of formulation F2**

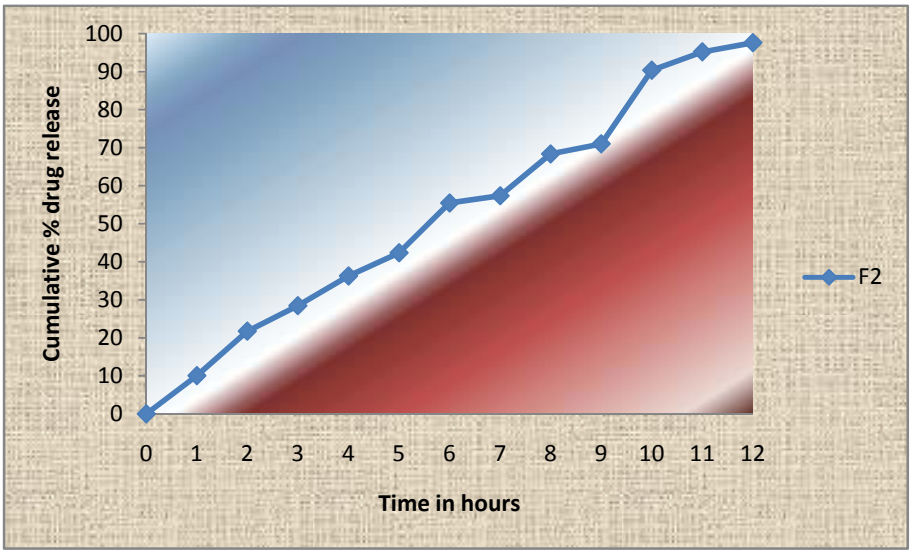


Figure 8.19: *In vitro* released graph of formulation F2

➢ **Dissolution profile of formulation F3**

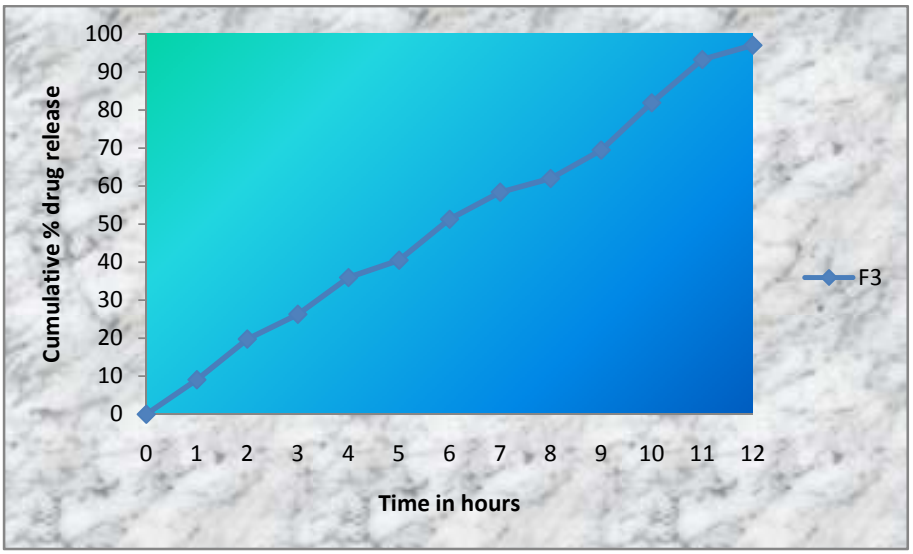


Figure.8.20: *In vitro* released graph of formulation F3

➢ **Dissolution profile of formulation F4**

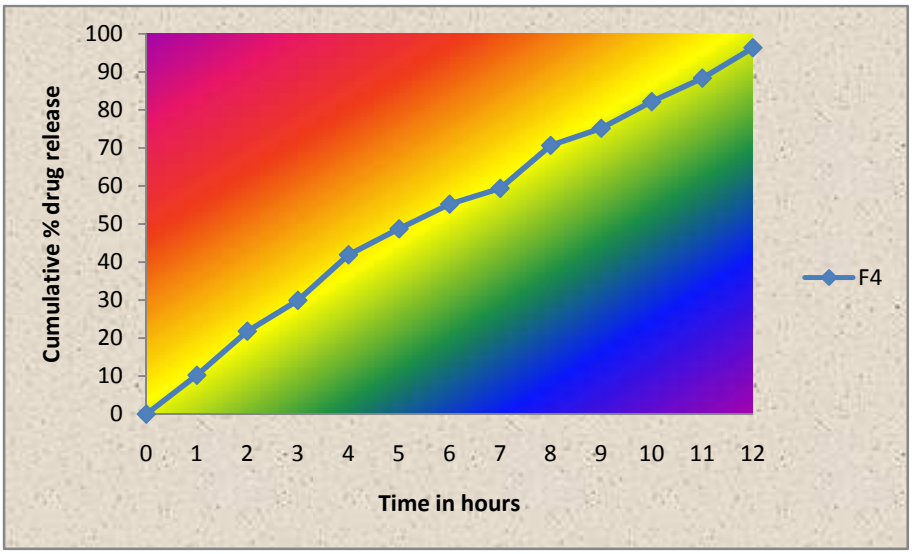


Figure 8.21: *In vitro* released graph of formulation F4

➢ **Dissolution profile of formulation F5**

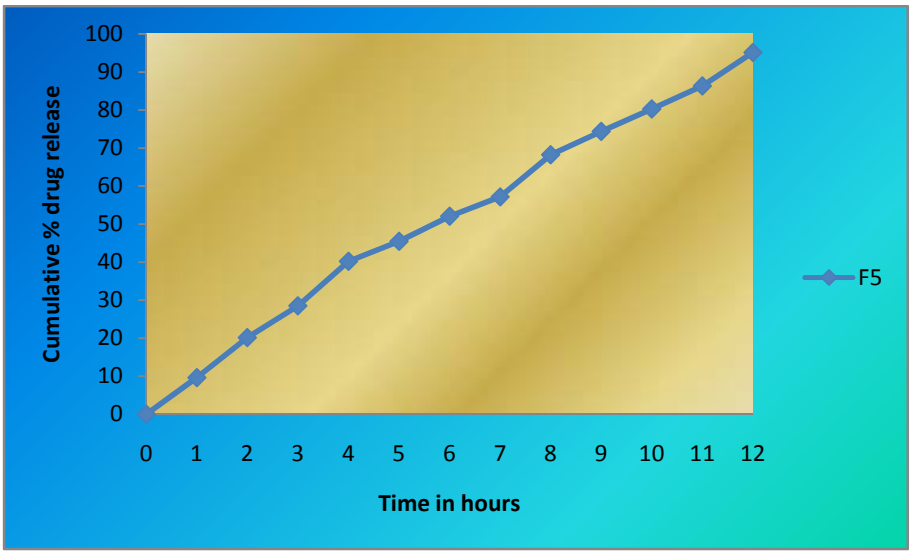


Figure 8.22: *In vitro* released graph of formulation F5

➢ **Dissolution profile of formulation F6**

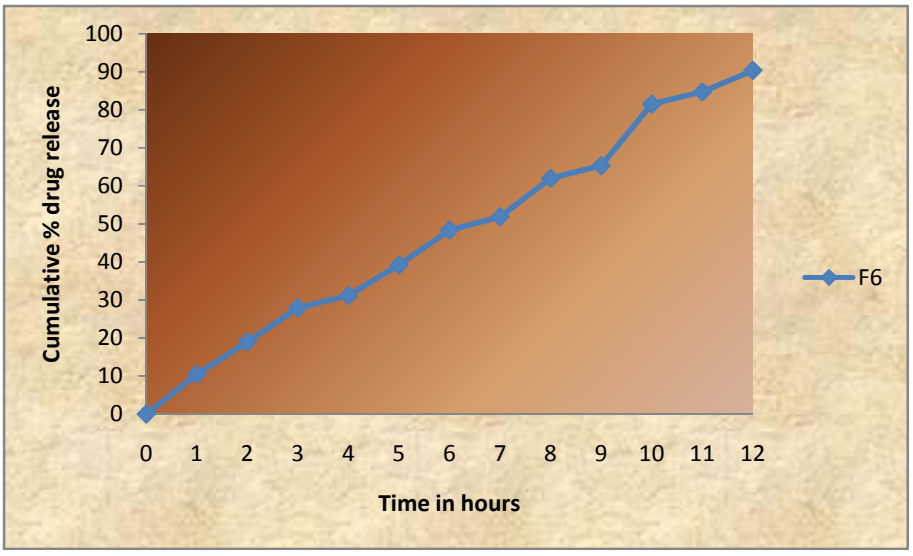


Figure 8.23 : *In vitro* released graph of formulation F6

➢ **Dissolution profile of formulation F7**

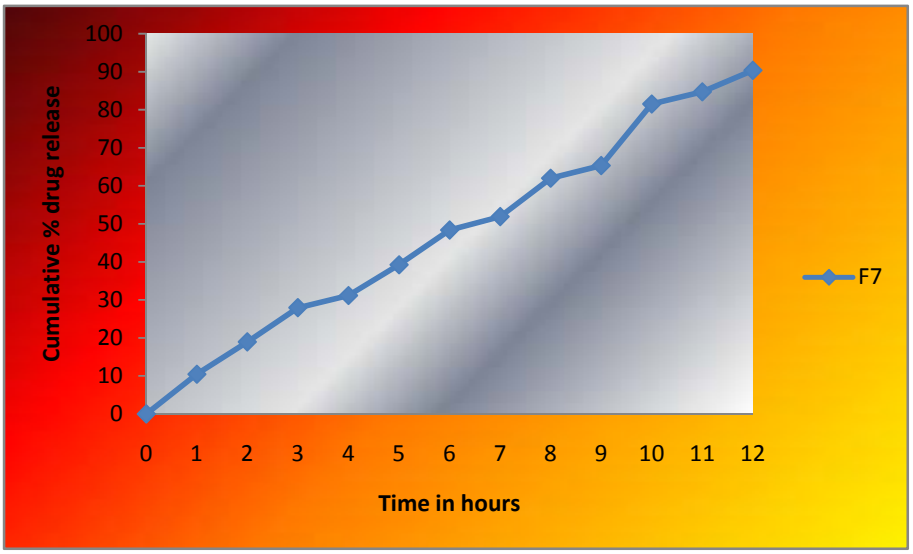


Figure 8.24 : *In vitro* released graph of formulation F7

➢ **Dissolution profile of formulation F8**

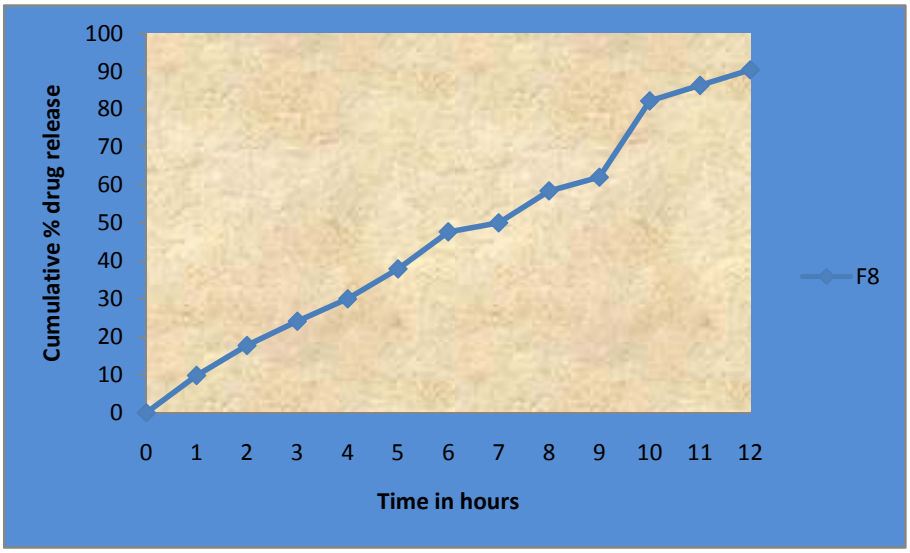


Figure 8.25: *In vitro* released graph of formulation F8

➢ **Dissolution profile of formulation F9**

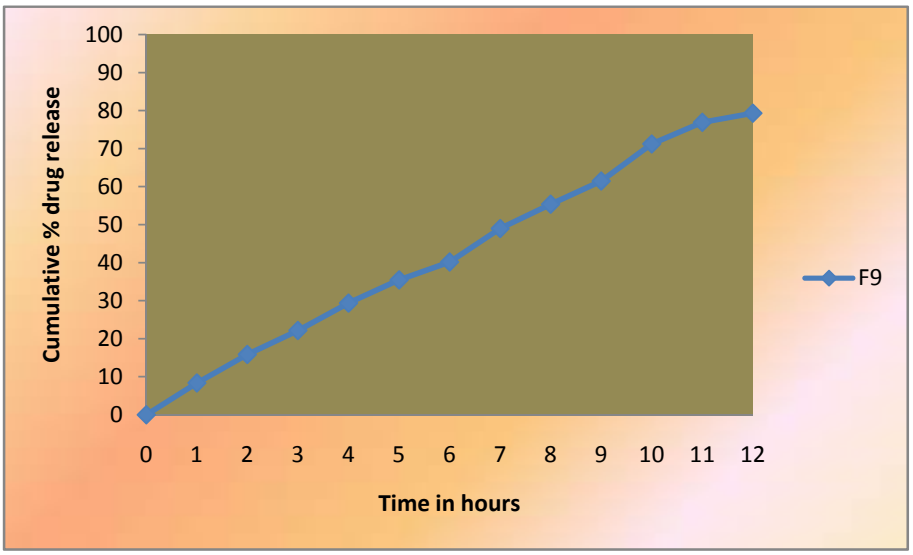


Figure 8.26: *In vitro* released graph of formulation F9

➢ **Dissolution profile of formulation F1-F9**

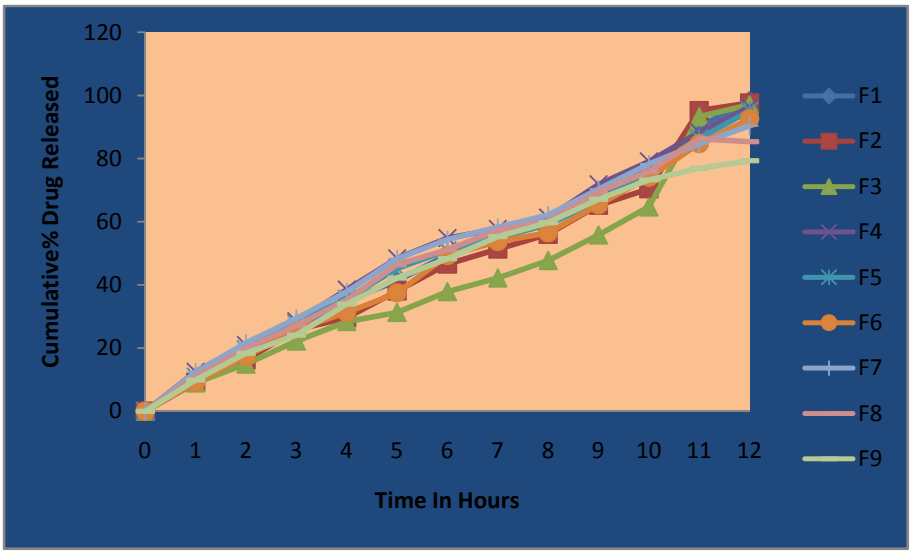


Figure 8.27 : Comparision of *in- vitro* drug released for formulations F1 to F9

From the *in vitro* drug released studies the formulations F1 - 98.36%, F2 - 97.62%, F3 - 97.04%, F4 - 96.35%, F5 - 95.14%, F6 - 92.37%, F7 - 90.37%, F8 - 85.37% and F9 - 79.30% were released the drug up to 12 hours.

Based upon the *in vitro* drug released profile the formulations F9 was chosen as best one among the formulations F1 to F9 were prepared. The formulation F9 released drug in sustained manner up to 12 hours compared other formulations

Table 8.14: Data of the percentage drug released at $t_{25\%}$, $t_{50\%}$, and $t_{90\%}$ values

S. No	Formulations	Time of % drug release(hours)		
		$t_{25\%}$	$t_{50\%}$	$t_{90\%}$
1	F 1	2.8	5.8	8.3
2	F 2	2.5	6.1	8.9
3	F 3	2.9	5.5	7.7
4	F 4	2.9	6.1	8.5
5	F 5	3.1	5.7	9.3
6	F 6	3.2	5.3	8.9
7	F 7	3.1	5.2	11.8
8	F 8	2.9	5.7	13.5
9	F9	3.1	5.9	13.7

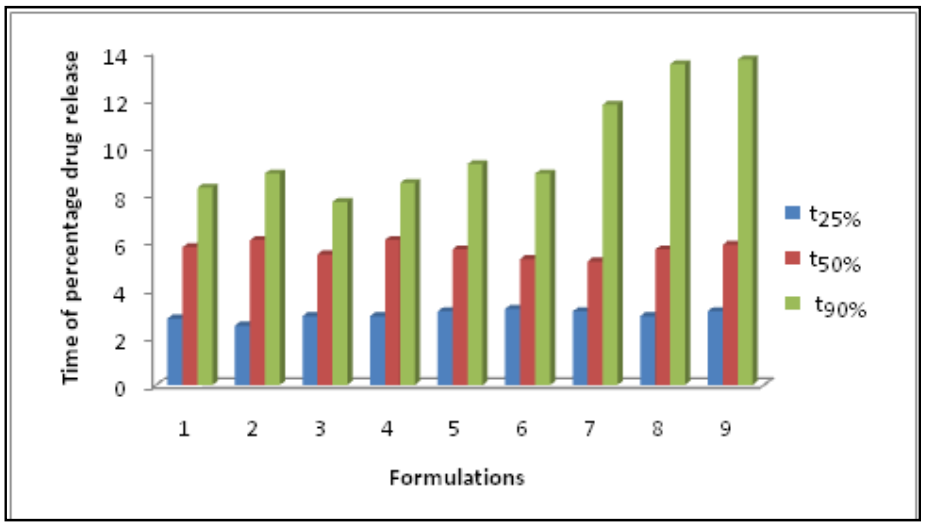


Figure 8.28: Comparision of *in vitro* drug released with $t_{25\%}$,$t_{50\%}$,$t_{90\%}$ values

8.2.7. Kinetics of Drug release

The kinetics of *In-vitro* drug release was determined by applying the drug released data to various kinetic models such as zero order, first order, Higuchi and Korsmeyer- Peppas. The result obtained was represented in Table 8.22 and shown in Figure 8.29, 8.30, 8.31, 8.32, 8.33, 8.34, 8.35, 8.36 and 8.37.

Table 8.15: *In vitro* drug released kinetics studies of all formulations

Formulation code	Zero order R^2	First order R^2	Higuchi R^2	Korresmayer Peppas		Best fit model
				R^2	n	
F1	0.992	0.752	0.947	0.995	0.4539	Peppas
F2	0.990	0.766	0.928	0.993	0.4437	Peppas
F3	0.994	0.752	0.925	0.995	0.5002	Peppas
F4	0.989	0.832	0.958	0.993	0.4771	Peppas
F5	0.992	0.894	0.951	0.995	0.4226	Peppas
F6	0.993	0.872	0.928	0.994	0.4588	Peppas
F7	0.993	0.872	0.928	0.994	0.3744	Peppas
F8	0.988	0.841	0.909	0.991	0.3481	Peppas
F9	0.997	0.939	0.930	0.998	0.3475	Peppas

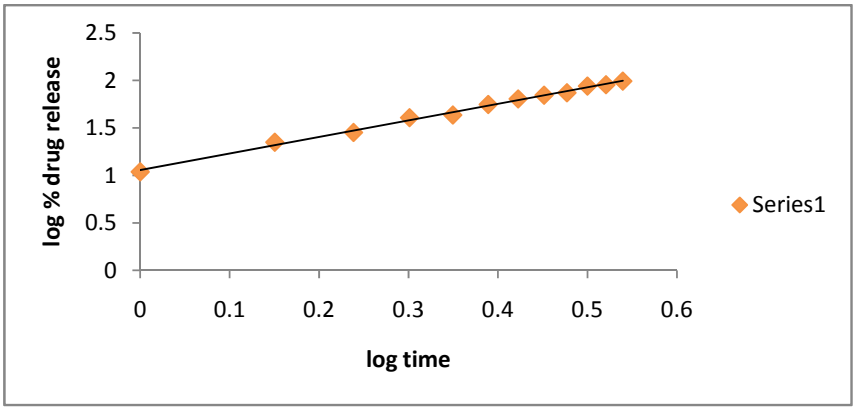


Figure 8.29: The best fit model (Peppas) of formulation F1

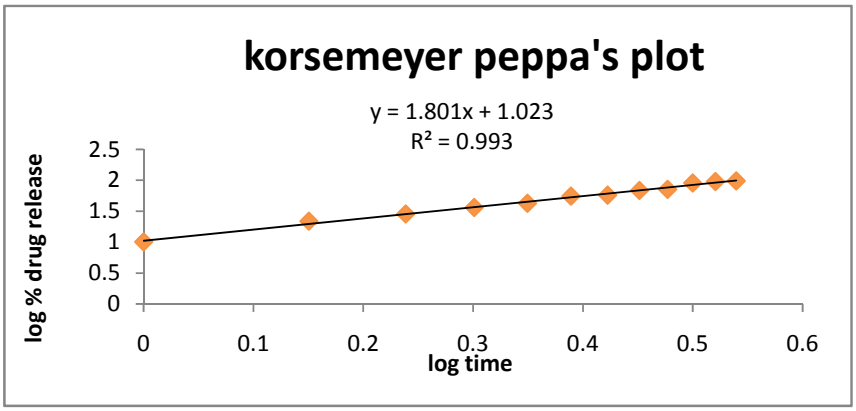


Figure 8.30: The best fit model (Peppas) of formulation F2

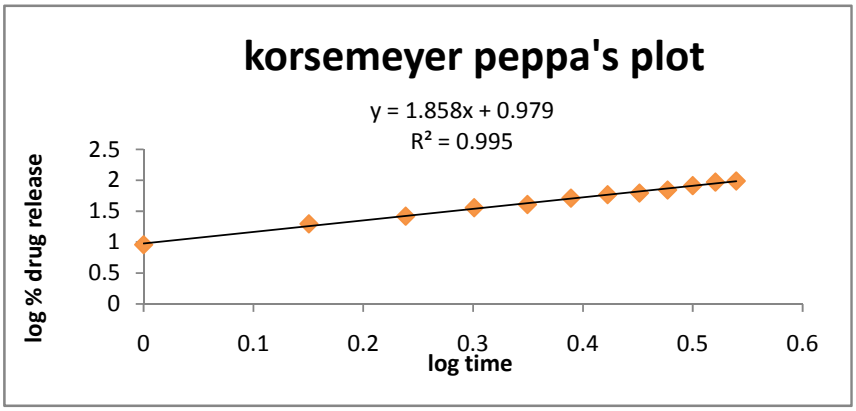


Figure 8.31: The best fit model (Peppas) of formulation F3

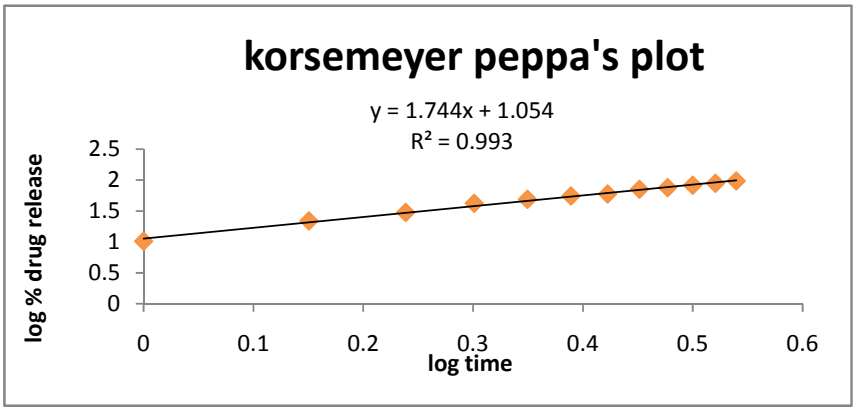


Figure 8.32: The best fit model (Peppas) of formulation F4

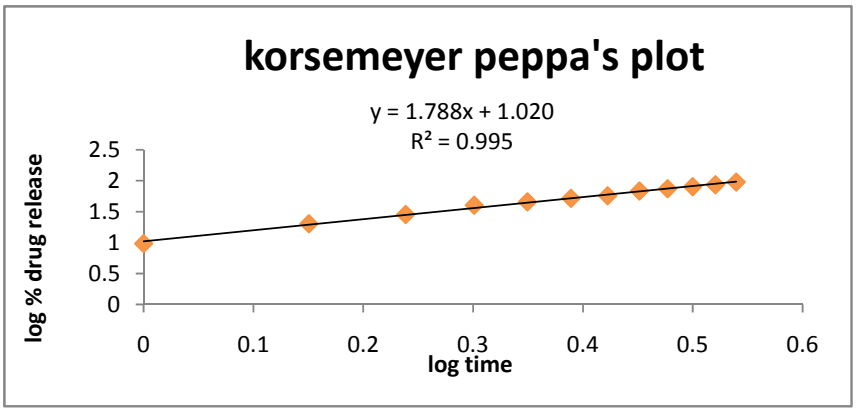


Figure 8.33: The best fit model (Peppas) of formulation F5

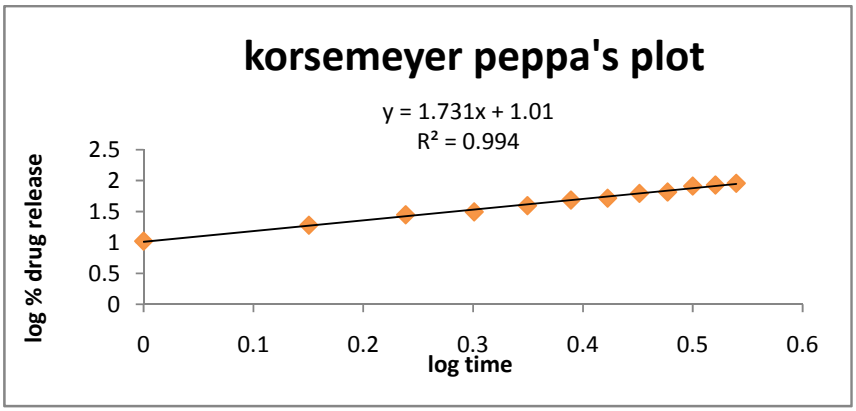


Figure 8.34: The best fit model (Peppas) of formulation F6

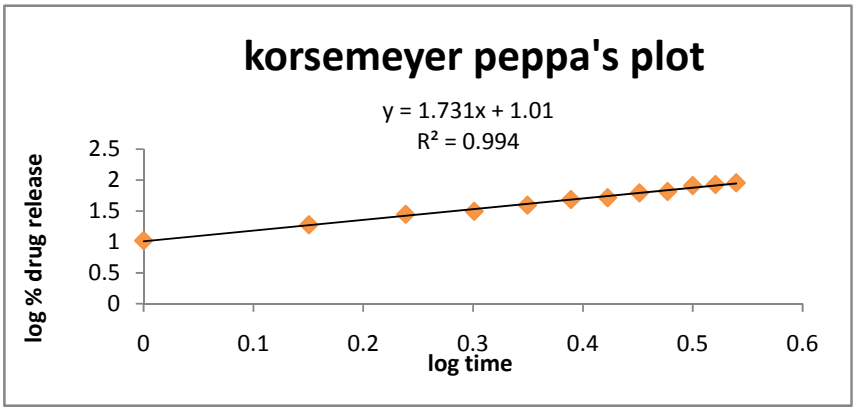


Figure 8.35: The best fit model (Peppas) of formulation F7

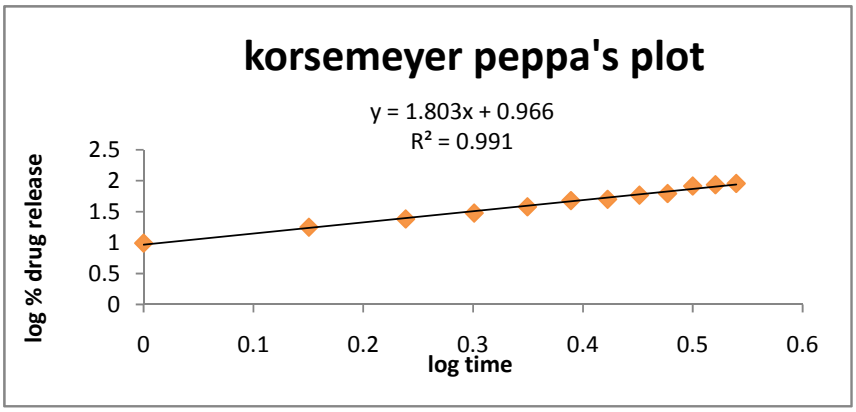


Figure 8.36: The best fit model (Peppas) of formulation F8

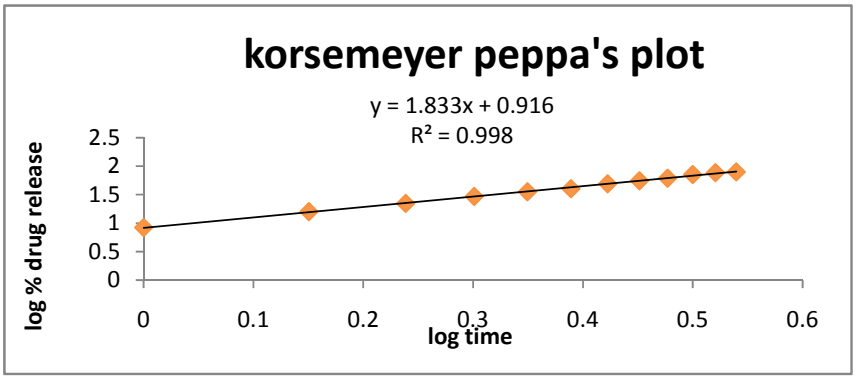


Figure 8.37: The best fit model (Peppas) of formulation F9

The drug released from the microspheres was diffusion controlled. The cumulative percent drug released versus the square root of time plots were found to be

a linear (r>0.99). The drug released profile of formulations, was shown by Fickian diffusion mechanism (n<0.5) and the best fit model was Korsmeyer-Peppas model.

8.3. STABILITY STUDY

The formulation F8 was observed after specified period stability studies as per ICH guidelines .The formulations was monitored for drug content and *In-Vitro* drug released profile and results were represented in Table 8.23 and percentage drug released profile was shown in Figure 8.38.

Table 8.16: Data of stability studies of formulation (F9)

Characteristics	Initials*	1 month*	2 month*	3 month*
Drug content (%)	43.730±0.15	43.454±0.18	42.454±0.038	41.848±0.07
In-vitro drug release for 12 hours	78.983±0.15	78.576±0.25	77.327±0.04	77.271±0.05

*All the values are expressed as mean± S.D., n=3

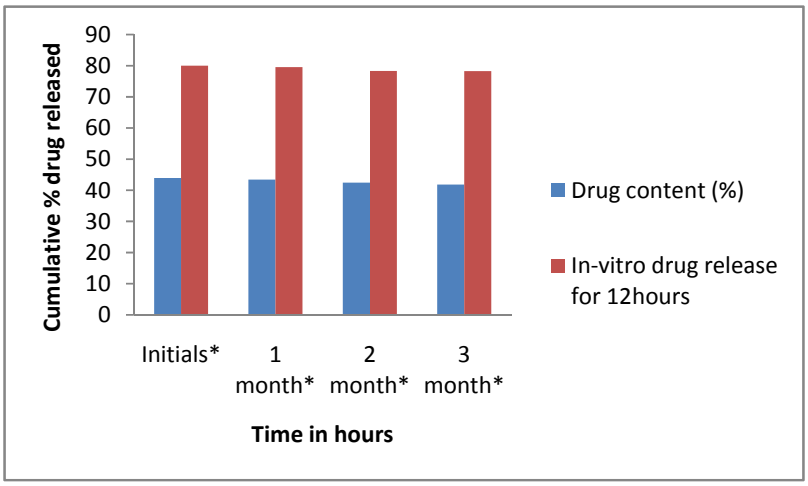


Figure 8.38: Cumulative % drug released after stability studies

There was no major difference found between before and after stability studies.

SUMMARY AND CONCLUSION

9. SUMMARY AND CONCLUSION

The goal of any drug delivery system was to provide the therapeutic amount of drug to the proper site in the body also to achieve and maintain the desired drug concentration in blood. Improving the therapeutic efficacy of existing drugs has been tried by different technologies. One of the effective technologies exiting in recent years of pharmacy is Microspheres.

Mucoadhesive drug delivery system was developed in pharmacy field and drug retention for a prolonged time has been achieved. Hence, it was made an effective attempt to formulate the mucoadhesive microspheres by using Quetiapine fumarate as the model drug it possess the mean half life of six hours and bioavailability was found to be only 9%. Hence, it was chosen as the good candidate for the mucoadhesive microspheres in order to improve the bioavailability and prolong period of drug released.

The identification of the drug was done by the FTIR spectroscopy analysis and drug polymers interaction was studied by DSC studies. It was concluded that no interaction was found between the Quetiapine fumarate and polymers.

Mucoadhesive microspheres of Quetiapine fumarate were prepared by Orifice-ionic gelation method. Drug-loaded mucoadhesive microspheres were composed of sodium alginate alone and in combination with HPMC K15M and carbopol 974p. For first three formulations F1, F2, F3 sodium alginate alone and F4, F5, F6 were composed of sodium alginate and HPMC K15M and F7, F8, F9 were composed of sodium alginate and carbopol 974p. From these formulations were evaluated for the particle size,

percentage yield, drug content and encapsulation efficiency, percentage moisture content, SEM analysis, *in vitro* wash off test, *in vitro* drug released, and stability studies.

The higher incorporation efficiency was observed as the concentration of alginate increased. This may be attributed to the greater availability of active calcium-binding sites in the polymeric chains and consequently the greater degree of cross linking as the quantity of sodium alginate increased, resulting in the formation of nonporous microspheres. The drug loading efficiency greatly improved when alginate was blended with carbopol at 1% level.

Mucoadhesive property of microspheres consisting of sodium alginate alone and in combination with HPMC K15M and carbopol 974p exhibited good mucoadhesive properties as. The wash-off was faster at simulated intestinal pH (6.8) than that at simulated gastric pH. Finally, reported that the solubility, hydration and mucoadhesivity of the polymers depend on the pH of the medium. The rapid wash-off observed at simulated intestinal pH may be due to the ionization of carboxyl acid group and other functional groups in the polymers, which increase their solubility and reduce adhesive strength. It would ensure the pro-long residence time at the absorption site to facilitate intimate contact with the absorption surface and thereby improve and enhance the bioavailability.

The in vitro drug release studies were carried out in the simulated intestinal fluid phosphate buffer pH (6.8). The microspheres were prepared by ionic internal gelation technique using calcium chloride as cross-linking agent. The microspheres cross-linked with calcium showed delay in disintegration and consequently a slow release of drug was

obtained. To retard or sustain the drug release from the microspheres, HPMC K15M and carbopol 934P were blended with the alginate matrix.

This kind of release is the characteristics of swelling-controlled system in which the rate of solvent uptake into a polymer is largely determined by the rate of swelling and relax-ation of the polymer chains. It is assumed that the drug molecules diffuse out through a dissolving gel-like layer formed around the drug during the dissolving process.

On comparing the major criteria in evaluation such as drug content, encapsulation efficiency, *in vitro* wash off test and *in vitro* drug release characteristics, the **formulation F9** was selected as the best formulation, as it showed the drug content as 43.96% and encapsulation efficiency was 87.70%, showed a good mucoadhesive nature in the *in vitro* wash off test was nearly 64.9% upto 8 hrs and *in vitro* drug released upto 12 hrs. Based on all the above evaluation parameters it was concluded that the formulation F9 was found to be best formulation among the formulations from F1 to F9. The mechanism of drug released was calculated by applying the kinetic models and it was concluded that the formulations F9 follows the Korsmeyer – Peppas model and it undergoes Fickian diffusion mechanism ($n \geq 0.5$).

According to the stability studies, the formulation F9 was found to be stable upto 3 months of storage period in drug content and *in vitro* drug released profile.

The **formulations F9** was concluded best formulation among the formulations were prepared.

FUTURE PROSPECTS

10. FUTURE PROSPECTS

In this present work, physio-chemical characterization and *in vitro* evaluation of Quetiapine fumarate Mucoadhesive microspheres were performed.

The following work had to perform in future:

- The microspheres can be also formulated by using other different mucoadhesive polymers.
- The mucoadhesive microspheres can also be formulated for advanced drug delivery other than oral administration.
- *In vivo* and *in vitro* correlation studies had yet to be performed and the results has to be determined .From the correlation results, it can serve as the model for humans and gain a better understanding of drug absorption and its dependence *in vitro* drug release.

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